HIV-associated neurocognitive disorders

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Summary

HIV infection is an important medical and social problem. In Poland, similarly to other countries, patients with HIV infection are mostly young people. Apart from typical immunological pathologies, HIV infection leads to some neurocognitive, motor and behavioral disorders. The aim of this paper is to present the up-to-date knowledge of HIV-associated neurocognitive disorders (HAND).

Key words: HIV-associated cognitive motor complex

Introduction

Neurocognitive disorders are common in patients infected with HIV (*Human immunodeficiency virus)*. HIV-dementia, HIV-associated dementia (HAD) and HIV encephalopathy (HIE) are terms used interchangeably since 1980 in order to describe a triad of disorders: cognitive, motoric and behavioral disorders in the course of HIV infection. They are currently defined by a more uniform system: HIV-associated neurocognitive disorder (HAND), which is aimed at identification of individuals who can undergo antiretroviral therapy (in accordance with the recommendations of the Polish Scientific Society AIDS (PSS AIDS) as well as European AIDS Clinical Society EACS – the implementation of antiretroviral therapy is recommended for individuals infected with HIV, diagnosed as having HAND, even if no other symptoms of the disease are present [1].

The introduction of highly active antiretroviral therapy (HAART) has led to a significant decline in the mortality rate of HIV-infected patients. As a result of HAART implementation, HAD incidence rate has also declined, however it does not provide full defence against the disease [2].

Epidemiological data

Since the onset of the epidemic, 68 million individuals worldwide have become infected with HIV, and approximately 30 million have died of AIDS. Approximately

34 million HIV-infected individuals were reported in 2010, as well as 2.7 million new infections and 1.8 million deaths caused by AIDS [1]. Every 6 seconds someone in the world contracts HIV, and every 9 seconds a person dies of AIDS-related causes [4].

According to the Epidemiology Unit of the National Public Health Institute, from the beginning of research in Poland in 1985 till 30 June 2012, HIV infection was found in 15,724 citizens, a total of 2,763 AIDS cases were reported; 1,162 patients died. At the same time it is believed that the real number of HIV-infected individuals in Poland might be twice or even three times larger than the number of documented cases [4].

In Poland, similarly to other countries, patients with HIV infection are mostly young people. 47% of all HIV infections affect persons between 20 and 29 years of age (7% were reported in persons below 20 years of age). 74% HIV-infected individuals and AIDS patients are at an economically productive age (20-49 years). In the first years of the epidemics in Poland, the major route of transmission for HIV infection was the use of intravenous psychoactive drugs as well as sexual contacts between males. However, since 2001 a change has been observed. Increasing numbers of individuals become infected through risky heterosexual contacts (currently the major route of transmission; one in four HIV infected persons is a woman), with no history of intravenous drug abuse. However, risky behavior frequently results from the use of psychoactive drugs other than intravenous drugs [4]. Data collected by Consulting and Diagnostics Centres (CDC), offering free and anonymous HIV testing, show that recently the number of infections in males who have sex with males (MSM) is rising alarmingly again [4].

Virus characteristics

HIV belongs to retroviruses of the genus Lentiviridae. The HIV particle is spherical in shape, is surrounded by lipoprotein envelope with glycoproteins – transmembrane gp41 and docking gp120 bonding non-covalently with gp41, through which gp120 particle is released to the environment and, just like HIV, may activate T lymphocytes.

HIV enters the cell with the participation of CD4 receptor and co-receptors (CCR5, CXCR4). CD4 receptors are located on the surface of lymphocytes, macrophages, precursor T-cells in the bone marrow and thymus, monocytes, eosinophils, dendritic cells and microglial cells in the central nervous system (CNS). CD4 bonding with gp120 leads to conformational changes, enabling the virus binding with the co-receptor and the virus envelope fusion with the cell membrane [5].

Gp120 is the most important immunological activator, activating macrophages and lymphocytes as well as inducing production of proinflammatory cytokines. It causes secretion of TNF-α by peripheral blood mononuclear cells, which stimulates HIV transcription. The increase in the levels of TNF-α is the most important primary disorder in the immune system, leading to progression of HIV infection [5].

Specificity of retroviral infection in CNS

A current theory says that HIV directly infects the brain tissue, which has been confirmed by detection of HIV in the central nervous system, its presence in the cere-

brospinal fluid and the virus visualization in the nervous tissue-infiltrating macrophages under the electron microscope which fuse and form multinucleated giant cells [6].

According to one of the "Trojan Horse" hypotheses, HIV enters the central nervous system by migration of the infected peripheral blood mononuclear cells across the blood-brain barrier (BBB), and then resides mainly in perivascular macrophages and microglial cells [7]. However, it is also possible that free virus particles penetrate into the brain directly across the BBB [7,8]. Evidence of HIV infection has also been found in astrocytes and oligodendrocytes. Although neurons appear to be uninfected, neurotoxic processes take place in them due to infection [7].

Following HIV penetration into CNS, the virus binds with cells containing CD4 receptor, causing – by irreversible connection with the calcium channel – the elevation of the intracellular calcium levels, as well as the increased production of neurotoxins and nitric oxide. It can also contribute to changes in glucose metabolism. After incorporation into the host genome in macrophages, it may lead to the release of more damaging compounds such as: quinolinic acid, superoxide anions, cytokines, eicosanoids, and may activate receptors for NMDA (*N*-Methyl-D-aspartate), which leads to neurotoxicity [6].

Microglial activation plays a crucial role in neuron impairment and resulting neurocognitive disorders in CNS in the course of HIV infection. Numerous studies have demonstrated a harmful role of Tat-protein [9]. Tat induces the elevation of intracellular calcium and mitochondrial reactive oxygen species (ROS) levels, which leads to calcium homeostasis disturbance and oxidative stress – nitric oxide production and nitric peroxide development, contributing to cellular death. In addition, Tat causes a delayed mitochondrial membrane depolarization, which suggests a significant role of membrane permeability in the process of Tat-induced apoptosis [10].

HIV proteins, including HIV envelope glycoprotein 160 (gp160), which splits into two non-covalently bound products (gp120 and gp41) as well as HIV Tat protein, display neurotoxicity potential. All these factors may disrupt neuronal and glial functioning, promote neurodegeneration and neuron death, which in turn leads to modification of synapse architecture in infected regions. The apparent HIV ability to interfere with progenitor neuronal cells may also disrupt regeneration mechanisms and neurogenesis in CNS. Moreover, an additional factor participating in the process of lymphocyte and nervous tissue deterioration is FAS protein and immunological factors, including TNFα [6].

The characteristic neuropathological lesions observed in autopsy examinations in HAD include encephalitis with astrocyte activation, multinucleated giant cells, microglia activation, monocyte infiltration, myelin sheath damage, and vacuolar myelopathy [7,11,12]. Myelopathy usually occurs simultaneously with HAD, but sometimes it develops prior to or without dementia symptoms, manifesting itself in the form of spastic paresis with sensory ataxia [13]. HIE may be found in any area of the brain.

Neuroimagining changes

The neuro-AIDS concepts arose between 1983 and 1988 [3, 14 -17]. The HIV-associated psychiatric and neurological clinical symptoms were defined, receiving a

general name of AIDS dementia complex (ADC) [14-17], HIV-associated dementia (HAD) [14-18], HIV encephalopathy (HIE) [19], or simply HIV-dementia [19-21]. Milder forms of HIV-related neurocognitive disorders are known as minor cognitive motordisorder (MCMD) [18] or, as emerged from the latest studies, HIV-associated mild neurovognitive disorders (MND) [22].

Examinations which can be used to reveal pathological processes in CNS turned out to be computer tomography (CT), magnetic resonance imaging (MRI) and cerebrospinal fluid analysis. These examinations should be performed in order to exclude opportunistic infections and other causes of cognitive disorders[6].

Magnetic resonance imaging (MRI) usually demonstrates both cortical and central atrophy and corresponding enlargement of the ventricles and sulci [9]. Moreover, signal enhancement can be observed in subcortical white matter in T2-dependent imaging. MRI reveals structural nervous system changes in patients who have somatic but not neurological symptoms [6].

HIE severity ranges from mild to severe cases with widespread inflammation and numerous giant cells. These changes may account for the observed range of clinical symptoms [23]. The presence of HIE correlates with HAD to some extent, occasional cases of HIE lesions were observed in autopsy examinations of patients with no clinical dementia symptoms intravitally [23].

HAD

HAD involves Tyree main areas: cognitive, behavioral and motor disorders [8, 12, 13, 14, 20, 24]. Commonly observed symptoms include: psychomotor slowness, apathy, bradykinesia, tremors and posture and gait disturbances (e.g. falls, stumbling) [25]. The initial cognitive symptoms frequently involve memory deficits, mental slowing, difficulty in reading and understanding [13]. The typical mental and neuropsychiatric HAD deficits are characterized by memory disorders (poor recall), impaired ability to use the acquired knowledge, changes in behaviour and general bradyphrenia [13]. In later stages, HIV-positive patients may also display attention deficits, disturbances of concentration, speech, executive function, information processing, and then motoricity. Other possible symptoms include social withdrawal, manic symptoms, organic psychoses with paranoid features, sleep disturbance (hypersomnia), confusion, or even delirium - a considerable variability of symptoms can be observed [12, 26]. Motoricity, executive ability and information processing rate are the cognitive functions which are most subject to decline from early infection to late stages of HIV [26]. Psychomotor slowness may be a predictor of the advanced occupation of CNS in the course of HIV infection, anticipating clinical HAD symptoms by 1-2 years[27].

In HAD, functioning ability declines in a changeable manner, which finally leads to withdrawal with severe, global dementia, often accompanied by vacuolar myelopathy and sensory neuropathy[28].

HAD is observed in approximately 10-15% of all HIV / AIDS patients, more often in the later stages of the disease [29]. In patients with the advanced stages of AIDS, HAD prevalence may reach 50%, and autopsy examinations show that as many as

90% AIDS patients may have HIE pathological index [12]. Milder forms of HAND are observed in 30-60% HIV-infected individuals depending on the stage of the disease [29, 30]. The average survival time of untreated HAD-patients is 6-9 months [12,20]. HAD may be the only manifestation of AIDS. HIV is probably the major cause of dementia in individuals below the age of 40 [31]. HAD constitutes an independent risk factor of death due to AIDS [11].

HAND

Diagnostics criteria for HIV-associated neurocognitive disorders have been revised twice. The final version was published in 2007 by National Institute of Mental Health (NIMH) and National Institute of Neurological Diseases and Stroke. The new HAND criteria have been divided into 3 categories:

I. HIV-associated asymptomatic neurocognitive impairment (ANI):

1. slight cognitive deficits in two or more neuropsychological domains,
2. cognitive function impairment does not affect daily functioning,
3. neurocognitive disorders fail to meet the criteria for delirium or dementia,
4. there is no evidence of pre-existing cause of ANI [22].

II. HIV-1-associated mild neurocognitive disorder (MND):

1. mild or moderate cognitive function impairment in two or more neuropsychological domains,
2. cognitive disorders affect, at east to a mild extent, daily functioning,
3. cognitive disorders fail to meet the criteria for delirium or dementia,
4. they are not conditioned by other concomitant diseases [22].

A patient may display mild concentration, attention or memory disturbances (e.g. complaints about difficulty in reading)

III. HIV-associated dementia HAD:

1. moderate or severe cognitive function impairment in two or more neuropsycholo-gical domains,
2. considerable difficulty in performing daily functions associated with intensification of cognitive disorders,
3. cognitive disorders fail to meet the criteria for delirium,
4. cognitive disorders are not conditioned by comorbid diseases [22].

The patient may develop speech problems, emotional shallowness, lack of spon-taneity and social withdrawal.

Neuropsychological diagnostics

Neuropsychological analysis is the key diagnostic factor. Appropriate screening tools are necessary in order to facilitate treatment implementation. As HAD is described as a subcortical process, the cognitive function impairment assessment requires the

examination of memorization, information storage and retrieval, the speed of mental and motor processes, information processing rate and precise motor function. Cortical syndromes may also appear, but at later stages of the disease and are more associated with opportunistic infection or neoplastic process [6].

Unfortunately, there are no neuropsychological tests designed specifically for HIV-infected patients. There is also no single diagnostic test aimed at HAND differentiation. The commonly used tests include: MMSE (Mini Mental State Examination), HDS (HIV Dementia Scale), IHDS (International HIV Dementia Scale) and Trail Making Test (TMT) [32]. According to the guidelines of PSS AIDS, the following neuropsychological tests are also recommended for HIV-infected individuals: Polish versions of Wechsler Adult Intelligence Scale (WAIS-R (PL)) and Wechsler Intelligence Scale for Children (WISC-R), Wisconsin Card Sorting Test (WCST), Verbal Fluency Test (VFT), Benton Visual Retention Test, Rey Complex Figure Test, Ruff Figural Fluency Test (RFFT), Attention and Observation Test, Combination Test, California Verbal Learning Test (CVLT), and Raven's Progressive Matrices test [33]. Although none of the tests is ideal, HDS seems to be the most useful.

HIV Dementia Scale (HDS) serves as a screening test in order to differentiate HIV-infected patients with dementia from HIV patients without dementia and to monitor the therapeutic effects. It is helpful for differentiating mild or moderate dementia from moderate or severe dementia. HDS is more sensitive than MMSE, considering subcortical effects of infection. It consists of four parts, which evaluate memory-recall, psychomotor speed, attention and construction. HDS sensitivity amounts to 80%, and its specific character amounts to 91% [34]. HDS has been criticized as some of its elements are difficult to perform for persons without neurological training [6].

It should be remembered that these scales are insufficient to diagnose dementia. Clinical symptoms of cognitive function impairment should also be taken into consideration.

Antiretroviral treatment

Treatment implementation is based on the patient's clinical condition, CD4 lymphocyte count and HIV viremia (copies/ml). According to the PSS AIDS guidelines, antiretroviral treatment is recommended for patients with symptomatic infection (category B or C in CDC classification) irrespective of CD4 lymphocyte levels or when CD4 level is lower than 350mmol/l, regardless of the severity of the disease. In asymptomatic patients, (category A in CDC classification), with CD4 cell count of 350-500 cells/mm3, the treatment needs to be implemented when the patient is over 50 years old with HIV RNA levels >100 000 copies/ml or when the patient is at a higher risk of cardio-vascular diseases, suffers from diabetes or CD4 cell count falls by 100 yearly. However, in pregnant women, patients with comorbid nephropathy, HBV or HCV coinfection, or with neoplastic disease, treatment is implemented at asymptomatic stages irrespective of CD4 cell count [35].

There are no guidelines on treatment of cognitive dysfunction or HAD. The main aim of the treatment seems to be suppression of the virus in plasma and CNS. As CNS

is considered to be the virus reservoir, it is necessary to use drugs penetrating blood-cerebrospinal fluid barrier [6].

A monthly therapy of HIV-infected patient in the Szczecin centre amounts to approximately 3500 zlotys [http://www.24kurier.pl/W-Kurierze/Przybywa-zakazonych].

Patients with HAD benefit from and should undergo antiretroviral therapy. Patients with MND may also benefit from HAART but the diagnosis and determination of cognitive disorder intensity needs to be clearly documented and confirmed by neuropsychological tests [1].

It should be remembered, however, that application of HAART is also associated with adverse effects on the part of central and peripheral nervous system. These effects may appear at different times of therapy. Due to the prolonged treatment period they are to be expected in almost all patients [36].

Complimentary treatment

Glycoprotein Gp120 may impair nerve cells by alteration of cellular calcium channels. It was demonstrated that particular calcium channel blocking drugs protect against the gp120 toxicity in vitro. Nimodipine is one of the drugs that has a protective effect and is used for regulation of intracellular calcium levels increase. Verapamil and diltiazem were demonstrated to be less effective than nimodipine, or not effective at all [37].

The use of memantine, N-methyl d-aspartate (NMDA) receptor antagonist, seems to be promising. The results of in vitro and animal studies demonstrate neuroprotective and gp120 neurotoxicity inhibiting effects [37].

Studies of rivastigmine use in HIV patients with undetectable viremia showed an improved psychomotor function. Transdermal form of the drug was better tolerated [38].

Attempts have been made to use minocycline in HIV-associated neurocognitive disorders. The latest research demonstrates that the use of minocycline has no significant effect on cognitive function improvement, compared with placebo [39].

There are also reports of intranasal insulin administration which has an effect on memory improvement in healthy adults and patients with Alzheimer disease. However, there is no evidence proving the method's effectiveness in HIV-infection dementia treatment [40, 50].

Conclusion

On the basis of the presented material it can be concluded that, despite the fact that the HIV-dementia incidence rate has declined since the introduction of highly active antiretroviral therapy, the prevalence of neurocognitive complications is rising due to ever increasing survival times of HIV patients.

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