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THERAPEUTICAL PRACTICE

NEUROCOGNITIVE IMPAIRMENT IN A NEWLY DIAGNOSED HIV POSITIVE PATIENT WITH ADVANCED DISEASE

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Abstract. Central nervous system involvement is relatively common in HIV infected patients ranging from subclinical neurological impairment to progressive dementia with a major impact on daily life and severe and potentially fatal opportunistic infections. We discuss the case of a newly diagnosed patient with advanced HIV infection presenting with neurological symptoms and a mild cognitive impairment. He had a low CD4 count (47 cells/mm3) and high plasma and cerebral spinal fluid viral loads (414.382 copies/ml and 141.040 copies/ml, respectively). The MRI showed symmetric periventricular white matter lesions. Findings were consistent with the diagnosis of HIV-associated mild neurocognitive disorder. New classification of the HIV-associated neurocognitive disorders and current treatment recommendations are also discussed.
Keywords: HIV-associated neurocognitive disorders

Introduction

Central nervous system (CNS) involvement is relatively common, 40% of HIV infected patients developing neurological complications during the course of the disease.

It can be caused either by the direct effect of HIV itself or indirectly through immune suppression and chronic inflammation.

The most frequent causes of diffuse nervous system damage are HIV-associated neurocognitive disorders (HAND), cytomegalovirus (CMV) encephalitis and progressive multifocal leukoencephalopathy (PML).

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Case Presentation

A 21-year-old male recently diagnosed with HIV infection was referred to our clinic for starting antiretroviral (ARV) therapy. During the past years he had recurrent respiratory tract infections and since 2002 recurrent episodes of herpes zoster virus reactivation (about 1-2 per year). The patient complained of having trouble walking, difficulties concentrating and changes in behaviour of recent onset. He denied any substance abuse.

On physical examination the patient was in no apparent distress, alert, oriented, readily answering the examiner's questions. He had no cranial nerve abnormalities, no focal neurological deficits; no involuntary movements were present, his muscle tone was normal and he had no loss of muscle strength. His gait was ataxic, employing a wide base of support, Romberg's test was positive. Deep tendon reflexes were increased, more pronouncedly at the lower extremities. He had a right-sided ex-

trapyramidal syndrome. No sensory deficits were identified. Addressing his complaint of having difficulties concentrating, a Mini Mental State Examination was performed, the patient scoring 24/30 points. A dysexecutive syndrome was also present. He had no neck stiffness, photophobia or fever.

The complete blood count showed a lymphopenia of 700 cells/mm^3, and slight anaemia (haemoglobin 12.7 mg/dl); the platelet count was within normal limits. His BUN, creatinine, blood glucose, liver function tests, serum electrolytes, lipids and coagulation tests were also normal. He had a CD4 count of 47 cells/mm^3 and an HIV viral load of 414.382 copies/ml. Hepatitis B surface antigen (HBsAg), antibodies against HBsAg and hepatitis C virus were absent. He tested negative for syphilis antibodies, he had anti-CMV IgG present and negative anti-toxoplasma IgG. The interferon-gamma release assay from tuberculosis-sensitized lymphocytes (Quantiferon-TB Gold) was negative. Resting electroencephalogram was normal. A lumbar puncture was performed. The cerebral spinal fluid (CSF) had: 40 cells/mm^3, 140mg/dl protein, glucose and lactic acid were normal and oligoclonal bands were absent. The CSF HIV viral load was of 141.040 copies/ml. PCR for CMV and the polyomavirus JC from CSF were both negative.

Cerebral magnetic resonance imaging (MRI) showed a mild cortical atrophy associated with high-signal white matter periventricular changes on T2 images (Fig. 1) and FLAIR weighted images (Fig. 2), iso-intense signal on T1 weighted images (Fig. 4), without mass effect, suggestive of HIV-induced CNS involvement. The presence of bilateral and symmetric low-signal on T2-weighted and FLAIR images in the globus pallidus suggested a possible associated metabolic disorder (Fig. 3). Moderate pansinus mucosal thickening was also detected on the acquired images. The second evaluation (3 months later) shows a moderate decrease of the high-signal white matter in the periventricular areas on FLAIR weighted images (Fig. 5), and no changes registered in the globus pallidus aspect (Fig. 6).

Considering that our patient presented with progressive neurocognitive impairment of relatively slow onset which was mildly interfering with the patient's daily activities, diffuse CNS involvement on MRI, had a high plasma and CSF-HIV viral load, and a very low CD4 count, he was diagnosed with HIV-associated mild neurocognitive disorder (MND). Treatment was started using lamivudine, zidovudine, lopinavir/ritonavir, a combination with

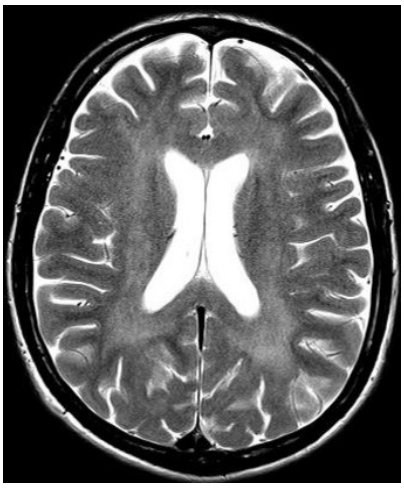

Figure 1. T2 weighted image

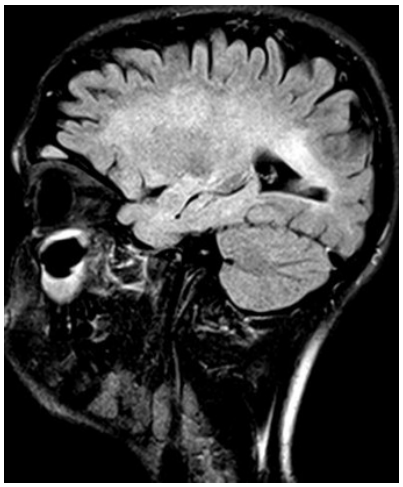

Figure 2. FLAIR weighted image

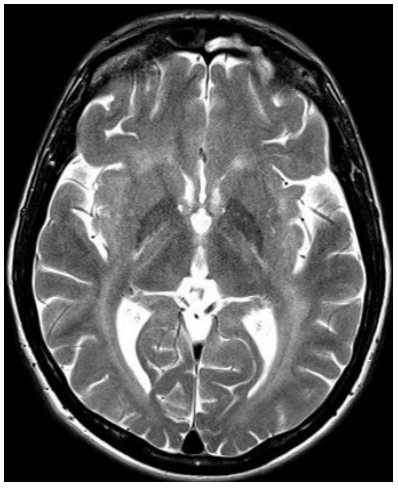

Figure 3. T2 weighted image

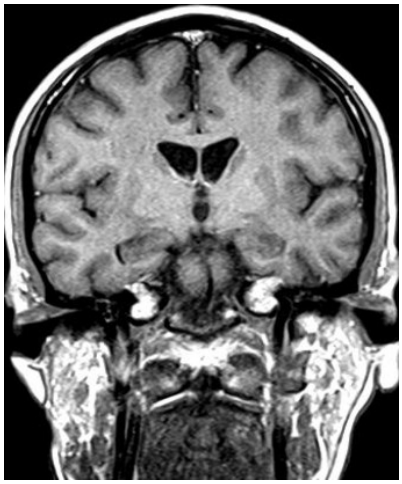

Figure 4. T1 weighted image

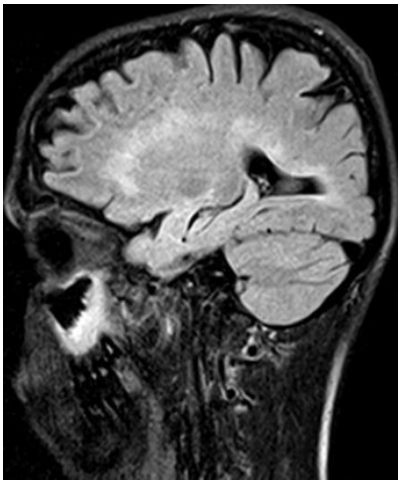

Figure 5. FLAIR weighted image

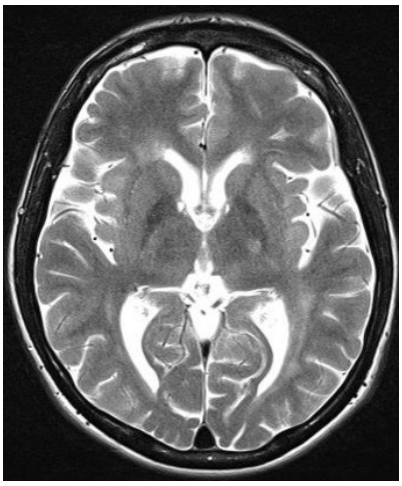

Figure 6. T2 weighted image

adequate CNS penetration. In addition to the ARV regimen, prophylaxis for Pneumocystis jirovecii pneumonia was also initiated.

At the next patient evaluation, one month after starting ARV therapy, his CD4 count had slightly increased (77 cells/mm^3), and his plasma and CSF viral loads dropped substantially reaching a plasma level of 1051 copies/ml (2.6 log reduction) and a CSF viral load of 328 copies/ml (2.6 log reduction). Three months after treatment initiation, his neurological symptoms had improved, but had not resolved completely, his plasma and CSF viral loads remained low, but still at a detectable level, and the diffuse cerebral lesions on MRI had subsided, allowing for a less frequent patient monitoring in the future. Treatment adherence was reportedly excellent.

Discussion

In HIV positive patients there are four major causes of CNS involvement. Focal cerebral lesions are masses within the brain that are usually visible on imaging studies, hence they can be ruled out in this case. Diffuse parenchymal damage can be caused by CMV, herpes virus and polyomavirus JC – considering the negative CSF-PCR results for the viruses and the pattern of lesions on the MRI (diffuse encephalitis with ependymal enhancement in the CMV disease; diffuse cerebral lesions, with primary involvement of hippocampus and temporal lobes and ependymal enhancement in CMV encephalitis and patchy, nonenhancing white matter lesions with frontal and parieto-occipital topography and involvement of subcortical U-fibres in the progressive multifocal leukoencephalopathy), it is unlikely that they are the pathogens in this patient. HIV itself can also lead to diffuse white matter involvement, and this is going to be discussed later on. Cryptococcal or tuberculous meningitis can also cause neurological symptoms, however in this patient the CSF was not indicative for either of the two – the India ink preparation and cultures from the CSF were negative. Other causes of neurocognitive impairment in HIV infected patients, but unlikely in this case, are depression, substance abuse, vitamin deficiency, thyroid disorders, and in the treatment experienced patients – ARV neurotoxicity. Causes of CNS involvement in HIV patients are reviewed in Table I.

HIV enters the CNS very soon after primary infection, probably inside infected monocytes/macrophages, and once there, the virus can infect

Meningitis • **Cryptococcus** • **Mycobacterium tuberculosis** • Cytomegalovirus • Lymphoma • Fungal infection • Syphilis • HIV **Spinal cord involvement** • Cytomegalovirus • Varicella zoster virus • Vacuolar myelopathy (HIV) • Toxoplasmosis (abscess) • Mycobacteria • Cryptococcus • Lymphoma	**Cerebral involvement** **Diffuse:** • **Cytomegalovirus** • **PML** • **HAND** • Toxoplasmosis • Herpes simplex virus **Focal lesions:** • **Toxoplasmosis** • **Lymphoma** • Cytomegalovirus • PML • **Tuberculosis** • Varicella zoster virus • Cryptococcus

Table I. CNS involvement in HIV infected patients[2]

Memory-Registration	
Give four words to recall (dog, hat, bean, red) – 1 second to say each. Then ask the patient to repeat all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.	
1. Motor Speed:	
Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.	4 = 15 in 5 seconds 3 = 11-14 in 5 seconds 2 = 7-10 in 5 seconds 1 = 3-6 in 5 seconds 0 = 0-2 in 5 seconds
2. Psychomotor Speed:	
Have the patient perform the following movements with the non-dominant hand as quickly as possible: Make a fist and rest it on a flat surface. Put hand flat on surface with palm down. Put hand perpendicular to flat surface on the side of the 5th digit. Demonstrate and have patient perform twice for practice.	4 = 4 sequences in 10 seconds 3 = 3 sequences in 10 seconds 2 = 2 sequences in 10 seconds 1 = 1 sequence in 10 seconds 0 = unable to perform
3. Memory-Recall:	
Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).	Give 1 point for each word spontaneously recalled. Give 0.5 points for each correct answer after prompting Maximum – 4 points.
Total International HIV Dementia Scale Score:	
This is the sum of the scores on items 1-3. The maximum possible score is 12 points. A patient with a score of ≤ 10 should be evaluated further for possible dementia.	Consider CNS nuclear magnetic resonance imaging, lumbar puncture including CSF HIV RNA measurement, and consultation with neurologist or neuropsychologist.

Table II. International HIV Dementia Scale (IHDS) – detects mild to severe neurocognitive impairment[1]

cells such as microglia, leading to immune activation and release of cytokines and viral particles within the brain[8]. HAND is thought to occur via two mechanisms[9]: on one hand the neurotoxicity as a consequence of direct HIV exposure and the indirect effect of neurotoxins released by infected or immune stimulated microglia and infiltrating peripheral macrophages, and on the other hand the HIV-induced impairment of neurogenesis, which can lead to the reduced ability to form new memories and learn new tasks[9,10].

The HAND, as defined by the HIV Neurobehavioral Research Center[3] can be classified, depending of its severity into three groups: 1) Asymptomatic neurocognitive impairment (ANI), 2) HIV-associated mild neurocognitive disorder (MND), and 3) HIV-associated dementia (HAD).

The MND is defined by the following features: 1) an acquired mild-to-moderate impairment in cognitive function on tests of at least 2 different cognitive domains (verbal; attention; abstraction; memory; complex perceptual-motor performance; motor skills), 2) the cognitive impairment interferes, at least mildly, with daily functioning, 3) the functional impairment has been observed for ≥1 month, 4) the impairment does not meet criteria for delirium or dementia, and it is not fully explained by other comorbid conditions (including opportunistic infections)[3].

The EACS recommends screening all patients suspected as having HAND using the International HIV Dementia Scale (Table II), and if neurocognitive impairment is detected and the patient is treatment naïve, therapy should be started using at least 2 ARVs with CNS penetration[1]. Another scale that can be used to assess severity of HAND is the Memorial Sloan Kettering (MSK) Scale (Table III), which combines the functional impact of both cerebral (dementia) and spinal cord (myelopathy) dysfunction. The two entities can be separated and staged independently[2].

Before highly active antiretroviral therapy (HAART), HAD was occurring primarily in patients with advanced HIV disease and low CD4 counts, being the presenting feature in 15-20% of newly diagnosed cases[4]. HAD is the most severe form of HAND, representing a major cause of dementia in the young. With the introduction of combined ARV therapy, the incidence of HAD decreased[5] however, in recent years a rise in HAND preva-

Stage	Degree of Severity	Description
0	Normal	Normal
0.5	Equivocal or subclinical	Absent, minimal or equivocal symptoms, without impairment of work or capacity to perform activities of daily living (ADL); mild signs, such as snout reflex and slowed ocular or extremity movements, may be present (gait and strength are normal)
1.0	Mild	Able to perform all but the more demanding aspects of work and ADL, but with unequivocal evidence of intellectual or motor impairment, which may include impaired performance on neuropsychological testing (tandem gait may be impaired but patient can walk without assistance)
2.0	Moderate	Able to perform basic activities of self-care but cannot work or maintain the more demanding ADL (ambulatory but may require single prop, eg. cane)
3.0	Severe	Major intellectual incapacity – cannot follow news or personal events, cannot sustain complex conversations, considerable slowing of all output – or motor disability (cannot walk unassisted, requiring walker or personal support, usually with slowing and clumsiness of arms as well)
4.0	End-stage	Nearly vegetative, intellectual and social comprehension and output are at a rudimentary level, nearly or absolutely mute (paraparetic or paraplegic with urinary and fecal incontinence)
Myelopathy staging in parentheses		

Table III. The Memorial Sloan Kettering Scale for AIDS Dementia Complex[2]

lence of mild and moderate severity was noted[6]. It is important to identify patients with HAND in order to optimise treatment, adherence, improve quality of life, and patient follow up, considering that HAND is an independent risk factor for death due to AIDS[7].

When considering treatment options in patients with HAND, it should be taken into account that drug concentrations in the CSF are different from those in the systemic circulation. This is due to the presence of the blood-brain barrier (BBB), an anatomical boundary separating the brain parenchyma from the systemic circulation, which regulates the transport of molecules from the blood supplying the brain[11]. It allows lipid-soluble compounds to diffuse across it, however polar compounds require an active transport to cross the BBB. It also limits the passage of many drugs including ARVs[11].

The CNS penetration-effectiveness rank (CPE) can be used to assess the degree of CNS penetration of a selected ARV regimen. Individual ARVs are grouped depending on their CNS diffusion level into four categories (Table III)[12].

There have been a number of studies in recent years investigating the degree of CNS penetration of different ARVs, in relation to CNS viral suppression and neurocognitive improvement, which showed that the good CNS penetrating drugs had a superior effect on the two vs other ARVs[13-16].

It is thought that ARVs act in two different ways to decrease neuronal damage: they reduce the chronic inflammatory response by means of controlling systemic viral replication, and suppress viral replication within the CNS[17].

Currently the use of good CNS penetrators is recommended when dealing with patients who are either treatment naïve, or experienced, but have some form of HAND[1].

The neurocognitive improvement begins early after starting ARV therapy and it becomes clinically meaningful after 24-36 weeks. Independent predictors for improvement are use of ARVs with high CPE rank, severe cognitive impairment, and perhaps also the extent of viral load reduction[15]. However the regression of the neurocognitive impairment is not expected to be complete in all patients since neuronal loss is thought to be permanent even when CNS inflammation is controlled[17] (Table IV).

There have been a number of adjunctive therapies which proved little or no success in improving the neurocognitive impairment, these include: selegiline, serotonin reuptake inhibitors, lithium, valproic acid[9,18,19]. Other options that need further evaluation are: minocycline, erythropoietin, insulin-like growth factor, neurotrophins, antibiotics, inhibitors of p38 MAPK and calcium channel blockers[9,20].

Considering that HAND is relatively common and can have a major impact on the quality of life, all patients complaining of neurocognitive impairment should be screened for the disorder and the ARV regimen should be tailored as to include drugs with good CNS penetration, if necessary.

	Best penetrators	**Moderately good**	**Moderately poor**	**Poor penetrators**
NRTIs	**Zidovudine**	Abacavir Emtricitabine	Didanosine **Lamivudine** Stavudine	Tenofovir Zalcitabine
NNRTIs	Nevirapine	Delavirdine Efavirenz	Etravirine	
PIs	Indinavir-RTV	Darunavir-RTV Fosamprenavir-RTV Indinavir **Lopinavir-RTV**	Atazanavir Atazanavir-RTV Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir-RTV Tipranavir-RTV
Entry/ Fusion Inhibitors		Maraviroc		
Integrase Inhibitors		Raltegravir		

Table IV. Classification of ARVs depending on the degree of CNS penetration (modified after Letendre, CROI 2010)12

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