Clinical Case

HIV associated Dementia, a case report

(Síndrome demencial asociado a VIH/sida. A propósito de un paciente)

Ricardo Boza-Cordero

Abtract:

HIV affects the nervous system producing different clinical manifestations, for which neuropsychological disorders are the most common. Up to 25% of autopsies have histopathological changes due to HIV. Currently it is considered that HIV-associated dementia (HAD) is the most common cause of dementia for people less than 40 years old. Diagnosing HAD is very important because it is considered an AIDS defining illness, its presence affects treatment adherence and antiretroviral drugs could revert its progress. Studying and following these patients should be based on clinical observation, neuropsychological analyses and neuroimaging. This case presents a 39-year-old male, who started with progressive memory loss and distal tremor; and diagnosed as an HIV associated dementia by clinical, neuropsychological and neuroimaging methods. Emphasis is placed on the pathophysiology of this disorder, the importance of proper diagnosis and the use of antiretroviral therapy.

Keywords: HIV/ AIDS, Dementia, HIV associated dementia, antiretroviral therapy

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Infectologist Physician, HIV/AIDS Clinic, San Juan de Dios Hospital. Associated professor at UCR (Universidad de Costa Rica) School of Medicine

Keywords: HIV, Human Immunodeficiency Virus; HAD, HIV associated dementia; CNS, Central Nervous System; SPECT, Single Photon Emission Computed Tomography; HAART, Highly Active Antiretroviral Therapy

Correspondence: Ricardo Boza Cordero
E-mail: ricardob49@hotmail.com

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Retroviruses, and particularly Human Immunodeficiency Virus (HIV), characteristically affect the immune and nervous systems with varied clinical manifestations.[1] Nervous lesions can be divided into those produced by secondary immunodeficiency-related opportunistic illnesses, such as meningeal cryptococosis, cerebral toxoplasmosis, Non-Hodgkin lymphoma, among others; those determined by the virus itself infecting brain tissue, and those related to antiretroviral treatment, such as Immune Reconstitution Inflammatory Syndrome. [2]

HIV is neuroinvasive (penetrates the CNS), neurotropic (can live in neural tissue) and neurovirulent (causes CNS disease). [2,3] Due to its strong neurotropism, it is possible to identify the HIV anywhere in the neuraxis, from the cerebral cortex to the neuromuscular junction; but the most affected site is the CNS, where changes are predominantly subcortical, including the deep white matter and basal ganglia. [2,4]

Since first AIDS cases described in the 80´s, it was seen that neuropsychological changes were the main manifestations of CNS compromise. [1,3] This is how it was demonstrated the presence of dementia as a direct patophysiological effect of HIV illness and as a chronic neurodegenerative process, with a variable frequency (15-50%) for different published series.

Currently, HAD is considered the most frequent cause of dementia for people less than 40 years old.[5] Neurocognitive disorders have a complex classification, however its demonstration by clinical, neuropsychological and neuroimaging methods is important, because HAD is considered and AIDS defining illness, its presence affects compliance with treatment and it has also been observed that antiretroviral drugs could revert its progress. [5,6]

An HIV/AIDS patient is presented, diagnosed with Dementia Syndrome by several psychological tests, CT-scan and SPECT changes, compatible with brain atrophy and HAD.

Case Presentation

A 39-year-old, costarican salesman, with incomplete college education, started in 1996 with control at the San Juan de Dios Hospital´s HIV/AIDS Clinic. At that time, he had a $TCD4^+$ cell count of 672 cells/mm^3 and was classified as having an asymptomatic HIV infection.

Following biannual controls through July 2006, did not show significant clinical changes, with $TCD4^+$ cell counts from 650- 550 cells/mm^3, with viral counts twice (1999 and 2004) lower than 2000 RNA copies/ml. He had no history of sexually transmitted diseases, with two non reactive VDRL tests. Negative serum tests for B and C hepatitis, CMV and Epstein Barr Virus. At the end of 2006 he complained of mild recent memory loss and fine resting hand tremor, reason why a brain CT scan was performed in February 2007. The CT scan showed mild to moderate diffuse subcortical brain atrophy, without space-occupying lesions. A 99m Tc-ethylcysteinate dimer brain perfusion SPECT showed hypoperfused cortical zones at the frontal, parietal, temporal and occipital areas (Figure 1). The $TCD4^+$ cell count at that time was 680 cells/mm^3. Folic acid and B12 vitamin levels were normal.

That same month a neuropsychological evaluation (performed at the Psychiatry and Mental Health service) using several tests showed "significant neuropsychological alterations in attention and concentration functions, as in verbal and visuospatial memory, compatible with dementia". The study at the Social Work service in 2005 and 2007 revealed "weak critical consciousness about his disease and without effective support networks. Absent to control appointments". The patient was proposed to start antiretroviral therapy (HAART), which he rejected. The last evaluation was made on July 2009. Insistence was made for him about the need to start HAART, which he rejected once again. The patient continued with an important recent and past memory, with a lot of difficulty to recognize his relatives and their names, his distal hand tremor persisted.

Discussion

There is enough evidence to say that HIV affects

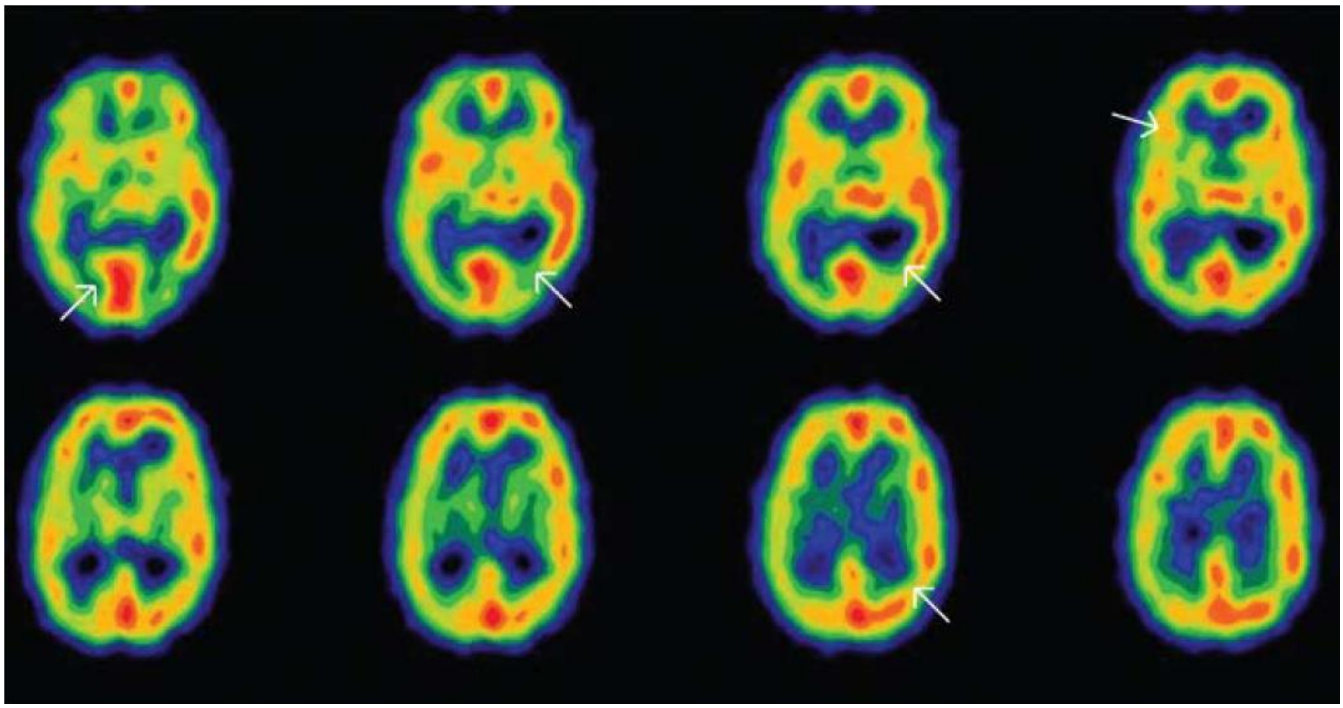

Figure 1. HIV Associated Dementia. 99m-Tc- ethylcysteinate dimer brain perfusion SPECT; temporally reoriented transaxial cut. Hypoperfusion areas are seen in the frontal, parietal, temporal and occipital cortexes (arrows).

the central nervous system in an early way, it could even be diagnosed within the first two weeks of the initial infection. [4] It follows the "Trojan Horse" model to enter this tissue, initially infecting circulating monocytes, which pass through the blood-brain barrier, carrying the viral proteins in their interior. [4,7]

There is no evidence of a direct neuron infection by HIV. [1,4] Therefore, the mechanisms involved in the neuropathogenesis are the lesion of the aforementioned support cells and inflammatory cytokines (tumor necrosis factor, free radicals, platelet activating factor, interleukin-1 and interferon-γ generated by one of these cells and with an autocrine, paracrine and endocrine action). [7,8] Besides, HIV-derived proteins, such as gp-120, are toxic to the surrounding neurons and the rest of glia cells. [4]

HIV has been identified mainly in the basal ganglia and the hippocampus.[8-10] It has been reported that the highest concentrations are reached in the globus pallidus, caudate nucleus and deep white matter. [4,7] In fact, the compromise at the caudate nucleus has a very important role in the development of neurocognitive disorders. [10] HIV-associated histopathological changes could be found in up to 25% autopsies, so that CNS compromise is second in frequency, exceeded only by pulmonary compromise. [2,4]

The most common manifestation of CNS HIV infection is a chronic neurodegenerative disorder, typified with cognitive, motor and behavior abnormalities, mainly apparent as attention/concentration, memory, learning and psychomotor speed deficits. [2,3,6] These neuropsychological disorders can be frequently associated with manifestations at the pyramidal and extrapyramidal (distal tremor, ataxia, incoordination) motor systems. [2]

The American Academy of Neurology recently established a nosology to classify these pathologies.[6] Briefly, neurocognitive disorders could be 1. Asymptomatic 2. Mild 3. HAD. To get more information about them, look at references 3,5 and 6. In general, these entities evolve progressively, just like HIV/AIDS. This is a diagnosis of exclusion, by ruling out delirium and other causes of dementia such as depression, tumors, cardiovascular disease or infections.

It is a clinical diagnosis, by psychological tests and neuroimaging.[1,5] Recently, a simple test has been developed, which can be used by health workers, to screen HIV/AIDS patients, and to refer those patients with low scores to the psychiatrist or psychologist.[11] The mini-mental test is considered to have a low value for these cases. For this patient, neuropsychological tests confirmed the diagnosis of HAD.[5]

Several studies have demonstrated a variable prevalence (15-50%) for these clinical entities.[2] Known risk factors are high viral loads, low $TCD4^+$ lymphocyte counts, anemia, age > 50 years old, intravenous drug use, female gender, among others.[3] Although HAD is more frequent in patients with $TCD4^+$ lymphocyte counts < 200 cells/mm^3 (constituting an AIDS defining illness), it could also be seen in patients with $TCD4^+$ lymphocyte counts > 350 cells/mm^3, as happened in this case.[1,3]

In Costa Rica, at San Juan de Dios Hospital, Quesada C and co-workers (not yet published data), made an analysis of 31 recently diagnosed HIV/AIDS patients, and applying the international HAD test, they found that at least 24 of these patients had some degree of cognitive compromise (77.42%). Seven (22.6%) did not have any secondary cause for the disorder, therefore classified as having HAD.

Most of them were men, and all of them had $TCD4^+$ lymphocyte counts < 200 cells/mm^3.

Since the introduction of HAART in 1996, many HIV/AIDS patients had an important clinical, virologic and immunologic improvement. These drugs demonstrated a lowering for both plasmatic and CNS viral charge, [12] watching an important decrease for this pathology´s associated complications, so that the incidence in HAD declined more than 50% since then. [2,3,5]

Robertson et al[13] studied 1160 HAART patients, 26% presented some neurocognitive impairment at

the initial evaluation. During follow up, 44% demonstrated an improvement with HAART. Similar results have been published by other authors. [5] A worrisome fact is that despite HAART, an important percentage of patients persist with neurocognitive disorders. There are multiple reasons for this, like treatment adherence, initial pathology severity, drug penetration into the CNS, duration of follow up, among others. [12]

Regarding the use of neuroimaging for managing these neurocognitive disorders, CT scan, SPECT and Magnetic Resonance Imaging (mainly functional), have been used, not just for diagnosis, but for HAART follow up. [14-18] SPECT has been useful because it allows to differentiate them from other types of dementia [15,16] and for some specific cases it has a larger sensitivity than CT scans and electroencephalogram (EEG) to detect brain lesions. [17] Using CT scan, MRI or SPECT for evaluating these patients has some disadvantages, such as the need to perform them at rest, regarding brain activity. Recently, studies such as several functional MRI types make a morphological and functional evaluation of the CNS, in subjects with specific brain activity, finding abnormalities even in those patients infected with HIV but without neurocognitive changes. [9,10,18]

For patients with some cognitive deficit and $TCD4^+$ lymphocyte counts < 200 cells/ml, the most frequent findings on CT scan and SPECT are brain atrophy and white matter abnormalities, which include focal areas of high intensity signaling, volume decrease and pallor, with a severity that is proportional to the regional virus concentration [16,17] as seen with this patient. White matter disturbances increase with disease severity; however these are not found in all symptomatic patients or with cognitive defects. [16]

On a multi-centric study[14] it was concluded that there is not enough evidence to establish a relationship between cortical atrophy and cognitive defects, and probably studies need a great sensibility to find any relation. However, caudate nucleus atrophy is correlated to neuropsychological disorders, and there is a contributory role for cortical and subcortical atrophy, but to an uncertain

Table 1: Protocol to investigate for HIV/AIDS associated Dementia.
San Juan de Dios Hospital

1. Clinical history: emphasis on short term memory disorders. Learning disorders. Apathy, irritability, depression, anxiety. Fine distal tremor. Licit and Illicit drug use.
2. Physical examination: emphasis on conscience, judgment, cranial nerves, tendon reflexes, praxis.
3. Laboratory exams: $TCD4^+$ lymphocytes, HIV viral load, TSH, hepatic function tests, blood cell count, folic acid serum levels, B12 vitamin, VDRL, CMV serology, monotest, B and C hepatitis serology, urine drug screening.
4. CT scan, EEG
5. Exclusion of other etiologies
6. International HIV associated Dementia Scale

The International Scale consists of three subtests, each of these subtests is rated on a scale of 0-4, being 0 the worst:

1. Finger tapping test: the patient is instructed to open and close the first two fingers of the non-dominant hand, as fast and wide as possible, over a 5 second period. A 0-4 score is given.

2. Alternating hand sequence test: the patient is instructed to perform a specific movement sequence with the non-dominant hand, as quickly as possible, and is quantified over 10 seconds to see how many repetitions are made. The sequence is:
   a. Clench the hand in a fist, on a flat surface.
   b. Put the hand on the surface, with the palm facing down.
   c. Put the hand perpendicular to the flat surface, lying on the cubital side.

Once the proceeding is explained and the examiner makes it himself, the patient has two opportunities to perform it. Later, the patient is told to do it as many times as he/she can, over 10 seconds. With a zero to four score.

3. Remembering four words after two minutes test: before the first test, four words are recited to the patient: red, dog, hat, bean. Each of the words should take 1 second to be said, and immediately the patient is told to repeat them; if this does not happen, the words are said again, until the patient repeats them correctly. The patient is the told that later he/she will be asked to repeat them again. At the third point of the test, the patient is asked to recall the words given at the beginning. For those words the patient does not guess, a semantic clue is given, for example: color (for red), animal (for dog), outfit (for hat) and vegetable (for bean). One point was given for each word recalled correctly and half a point for each clue-guided guess. Four points maximum.

At the completion of the test, the highest possible score is twelve, and all patients with ten or less points should be evaluated for dementia. With this cutpoint, the test has 80% sensitivity, and a 55% specificity.

7. Psychiatrist referral

level. In fact, by functional studies, it has been demonstrated that HAD diagnosis must be made by finding caudate nucleus atrophy, and not by determining the volume of white matter.[10] Therefore, the presence of cortical or subcortical atrophy does not imply HAD.

From the point of view of neuroimaging, some studies have demonstrated an improvement with HAART. However, the presence of disorders despite HAART, should not be interpreted as a therapeutic failure, as these drugs are frequently associated to an inflammatory phenomenon at the CNS.[12] Likewise, brain atrophy does not always have clinical nor neuropsychological repercussions.[15]

In summary, the correlation with different imaging diagnostic methods is useful for both diagnosis and antiretroviral therapy follow up.

The clinical correlation between several psychological tests, imaging studies and anatomopathologic lesions, has allowed a better comprehension of this entity. HAD is an exclusion diagnosis as with this patient, and its management, besides pharmacologic treatment, should include an interdisciplinary team with a psychiatrist, a psychologist and a social worker with an effective participation, as this is a complex pathology within HIV/AIDS own complexity.

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Translated by: Dr. Javier Estrada Zeledón