Short Report

Relation of cerebrospinal fluid/plasma HIV-RNA discordance with neurocognitive impairment


ABSTRACT

Neurological involvement is common in patients infected with HIV. The effectiveness of antiretroviral drugs in lowering the levels of HIV-RNA in cerebrospinal fluid (CSF) is limited by their inability to cross the blood–brain barrier. Discordance in CSF/plasma HIV-RNA levels may have a bearing on the progression of neurological disease in these patients. We report a woman with subacute neurocognitive impairment and abnormal findings on brain MRI, in whom there was a discordance between CSF/plasma HIV-RNA levels. The patient improved after a change in her highly active antiretroviral therapy (HAART) regimen. We also reviewed the available literature on the subject and found seven articles describing 27 patients.


INTRODUCTION

Nearly 40 million people worldwide are infected with HIV. Before highly active antiretroviral therapy (HAART) was adopted, HIV-associated neurocognitive disorders (HAND) occurred in about 50% of unselected cohorts. This has changed with the advent of HAART.

In some cases, however, HIV-1 replication remains high in the cerebrospinal fluid (CSF) in spite of viral suppression in the plasma. A possible relationship of this phenomenon to HAND has been postulated. Persistent viral replication in CSF and the ensuing high HIV antigen expression in the central nervous system (CNS) may be associated with HAND due to apoptosis and synaptodendritic HIV-induced injuries. Additionally, high HIV-RNA levels in CSF have been associated with HIV encephalitis, regardless of the concomitant presence of opportunistic diseases and the plasma viral load.

The finding of different resistance profiles of the virus in plasma and CSF isolates suggests that CSF and plasma are immunologically and virologically distinct compartments. It also stresses the need for complete suppression of HIV replication in CSF as well as in plasma. In cases of virological failure, it might be useful to investigate the CSF compartment to look for potential resistance, especially in patients with new neurological symptoms.

We report a patient with subacute neurocognitive impairment and CSF/plasma HIV-RNA load discordance. We also reviewed the published articles on this subject.

THE CASE

A 36-year-old previously healthy woman had been diagnosed to have HIV (B2 stage) 5 years ago when she presented with weight loss and genital molluscum contagiosum. Her husband had died earlier of AIDS-associated pneumocystosis. At that time her HIV-RNA viral load was 12 469 copies/ml and her CD4 count was 56 cells/cmm (6.4%). She was started on HAART with emtricitabine/tenofovir (FTC/TDF) and saquinavir/ritonavir (SQV/r). She showed plasmatic viral suppression after 2.5 years of HAART and remained stable during the following years (Table I).

One month before admission to the emergency service of our hospital, she developed sudden fever and headache associated with nausea, vomiting and recurrent episodes of inattention. Neurological examination at admission revealed abnormalities in higher mental functions, attention and verbal production, suggesting moderate frontal cortical dysfunction. No other focal neurological or meningeal signs were found. A CT scan of the brain was normal.

A lumbar puncture was done and the CSF showed glucose 48 mg/dl, proteins 260 mg/dl and 251 cells/cmm. She was started empirically on ceftriaxone, acyclovir and dexamethasone. Bacterial culture, Gram-stain, Ziehl–Neelsen stains, as well as India ink and cryptococcal latex agglutination tests on the CSF were negative. Serology for antitoxoplasma antibodies was also negative. Transcranial Doppler showed no evidence of secondary vasculitis, and an electroencephalogram (EEG) showed moderate-to-severe frontal dysfunction without seizure activity.
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a hyperintense lesion in the right occipito-temporal region (Fig. 1A and B). Gadolinium-enhanced MRI did not show abnormal enhancements (Fig. 1C).

Neuropsychological assessment (Neuropsi attention and memory test, Barcelona test, Complex Rey figure, and trail making test) showed moderate alteration in the attentional volume and generalized slowing; recovery failures were observed in sequencing, planning and monitoring executive processes. These findings suggested right frontal and temporal lobe dysfunction. The patient scored 18 points in the Montreal Cognitive Assessment (MoCA) test, version 7.1.

Following dramatic improvement with the above empirical treatment, the patient was discharged. One month later, during an outpatient follow-up visit, the HIV viral load was 88 RNA copies in plasma and 2046 copies in the CSF, with a logarithmic difference of 1.37 (CSF/plasma discordance). An HIV genotyping test was done in the CSF and plasma samples and showed several mutations (M184I in CSF and M184I and L10I in plasma).

Based on these results, her HAART regimen was changed to zidovudine and lamivudine (combivir) and lopinavir/ritonavir (kaletra). Two weeks later, a second neuropsychological assessment (Weschler adult intelligent scale, Complex Rey figure test, Barcelona test, phonemic and semantic fluency test, trail making test, BECK depression inventory, and Iowa gambling test) revealed only slight depressive symptoms, and on the MoCA test version 7.1 she scored 30 points.

A repeat MRI of the brain showed resolution of the previous hyperintense areas in the brain (Fig. 1D–F).

DISCUSSION

Literature review

We found 14 articles on HIV load in plasma/CSF. Of these, only 7 articles (which included 27 patients) had adequately described and evaluated neurological symptoms and signs. We analysed these 7 articles (Table II).

After hospital admission, the HIV viral load was 22 850 RNA copies/ml (log 4.36) in plasma and 889 740 RNA copies/ml (log. 5.95) in CSF, with a logarithmic difference of 1.59 (CSF/plasma discordance); CD4 lymphocyte count was 97 cells/cmm (12%). The patient was in virological failure in spite of good compliance with ART. Considering the low CD4 count, trimethoprim–sulphamethoxazole (TMP–SMX) and fluconazole were started as prophylaxis. MRI on FLAIR and T2-weighted sequences showed

![Fig. 1 A to F. Sections from MRI of the brain](image)

A and B: Axial FLAIR sequences at hospital admission showing occipito-temporal white matter hyperintensity; C: axial gadolinium-enhanced section shows no abnormal enhancement; D and E: axial FLAIR sequences 1 year after admission showing resolution of previous abnormal hyperintensities; F: axial gadolinium-enhanced MRI 1 year after admission shows no abnormal enhancement.

![TABLE II. Previous cases where CSF/plasma HIV discordance has been reported](table)

<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>At AIDS diagnosis</th>
<th>Initial HAART</th>
<th>Neurological manifestations</th>
<th>At neurological impairment</th>
<th>Neuroimaging findings</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Plasma HIV load</td>
<td>CD4+ cells/cmm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jenny-Avital and Chuang (2002)*</td>
<td>34/F</td>
<td>2199</td>
<td>192</td>
<td>LPV/r, 3TC, ABC</td>
<td>Tremor, cognitive impairment</td>
</tr>
<tr>
<td>Hull et al. (2006)*</td>
<td>44/M</td>
<td>5</td>
<td>ND</td>
<td>IDV, NFV, DLV</td>
<td>Moderate cognitive impairment</td>
</tr>
<tr>
<td>Garvey et al. (2009)*</td>
<td>33/M</td>
<td>361 837</td>
<td>190</td>
<td>ABC, 3TC, SQV/r</td>
<td>Gait and cognitive impairment</td>
</tr>
<tr>
<td>Canestri et al. (2010)*</td>
<td>50/ND</td>
<td>ND</td>
<td>250</td>
<td>TDF, FTC, ATV</td>
<td>Headache</td>
</tr>
<tr>
<td>49/ND</td>
<td>ND</td>
<td>4</td>
<td>AZT, 3TC, T20</td>
<td>Memory impairment, cerebellar ataxia</td>
<td>50</td>
</tr>
<tr>
<td>43/ND</td>
<td>ND</td>
<td>52</td>
<td>3TC, ABC, IDV/r</td>
<td>Cerebellar dysarthria and ataxia</td>
<td>50</td>
</tr>
<tr>
<td>50/ND</td>
<td>ND</td>
<td>221</td>
<td>TDF, FTC, DRV/r</td>
<td>Tactile allodynia</td>
<td>78</td>
</tr>
<tr>
<td>36/ND</td>
<td>ND</td>
<td>55</td>
<td>3TC, ABC, TDF, DRV/r</td>
<td>Coma</td>
<td>50</td>
</tr>
</tbody>
</table>

(continued)
The mean (SD) age of the patients was 47.9 (9.2) years; 3 were women, 13 men and no information was available for 11 patients. In 8 patients, there was previous disease: opportunistic infections in 2 (cryptococcal meningitis and *Pneumocystis jirovecii* pneumonia), and infection by a hepatitis virus in 6 (hepatitis B virus in 2, hepatitis C virus in 3, and both viruses in 1 case).

Clinical and neuroimaging findings

Cognitive impairment was seen in 19, headache in 2 and others (coma, ataxia and motor impairment) in 6. Neuroimaging (MRI) data were available in 24 patients: brain white matter hyperintense areas were seen in 22 and spinal white matter hyperintense areas in 2.

CSF cytochemistry

At the time of neurological complaints, the results of CSF examination were available for 16 patients. The mean (SD) CSF glucose level was 61.40 (28.80) mg/dl; CSF protein level was 106.2 (61.6) mg/dl and the CSF cellularity was 32.25 (48.96) cells/cmm.
**CSF/plasma HIV-RNA load and CD4 lymphocyte count**

At the time of diagnosis of HIV, the mean (SD) plasma HIV load of only 6 patients was available and was 4,000 461.83 (7,369 426.82) copies/ml (log$_{10}$ 4.58 [2.3]). The initial mean (SD) CD4 lymphocyte counts in 26 patients was 92.42 (86.94) cells/cmm.

At the time of neurological complaints, the plasma HIV load was 391.81 (1405.5) copies/ml (log$_{10}$ 2.2 [0.48]) and the mean CSF HIV load was 13 625.81 (50 749.53) copies/ml (log$_{10}$ 3.35 [0.69]). The mean CD4 lymphocyte count was 401.52 (171.99) cells/cmm.

**Viral resistance and CNS penetration**

HIV genotyping data were available in 21 patients: isolated HIV mutations were observed in 7 patients (NRTI3, NNRTI1 and PI3); more than one mutation was observed in 12. Absence of mutations was reported in 2 patients. The most frequent mutations were E44D, M41L, L210W and M184V.

**Clinical outcome**

The final clinical outcome was available for 15 patients: 2 patients died and 13 survived; despite adjustments in HAART, 3 patients did not improve. The final clinical outcome was available for 15 patients: 2 patients died and 13 survived; despite adjustments in HAART, 3 patients died and 13 survived. However, in some cases in spite of a reduction in plasma HIV viral load, a residual viral replication may persist in some anatomical reservoirs. One of these reservoirs is the CNS, a highly specialized microenvironment. Successful treatment of HIV requires suppressing viral replication in all body tissues. CNS is not only an anatomical viral reservoir, but could also be prone to persistent infections due to the blood–brain barrier (BBB), which may partially restrict the movement of many antiretroviral drugs from blood into CNS.

Polis et al. described HAART-naïve patients receiving a four-drug regimen; after 2 months of therapy, only 36% had successful CSF HIV-RNA suppression with levels <50 copies/ml. This suggested the possibility that replication continued leading to neurological disorders. On the other hand, high CSF HIV-RNA levels predict the onset of neurocognitive disorders, while viral suppression leads to an improved cognitive performance. Arbitrarily, it has been considered that CSF viral escape occurs when HIV-RNA plasmatic level is ≤50 log$_{10}$ copies/ml and CSF RNA level ≥1 log$_{10}$ higher than plasma RNA level.

Our review of the literature found a mean (SD) value for CSF RNA of 1.37 (0.41) log$_{10}$ higher than the plasma viral RNA level, confirming CSF viral escape in this population in spite of a mean CD4 lymphocyte count of 401.52 (171.99) cells/cmm. Men predominated and cognitive impairment was the most frequent neurological problem. CSF examination showed an inflammatory profile with lymphocytic pleocytosis and hyperproteinorachia.

Chronic infection with HIV affects various signalling pathways in the CNS, resulting in both apoptosis and synaptodendritic injury. Several HIV proteins by themselves can damage neurons and interfere with CNS function; gp 120, for instance, not only plays a role in virus infectivity but also interacts with host cellular receptors, inducing glutamate-mediated excitotoxicity, which could trigger a cytokine storm or caspase cascade.

Additionally, TNF-alpha is actively released by infected lymphocytes and glial cells; in vitro, it can cause glial cell activation, neurotoxicity, mitochondrial dysfunction, dendritic loss and neuronal death. Along with the toxic effects of HIV itself, secondary effects on the immune system could amplify neurological damage leading to progressive neurodegeneration.

The AIDS-related dementia complex, a subcortical dementia, is a progressive disabling disorder characterized by loss of attention and concentration, notable motor slowing and various behavioral components; it usually leads to death within 1 year. This syndrome was associated with pathological changes in the brain, including generalized atrophy, changes in the white matter causing leukoencephalopathy, microglial nodules typical of viral encephalitis, and multinucleated giant cells that appear as infected directly by HIV on antigen staining.

High HIV-RNA levels in CSF are associated with neurological disease: primarily cognitive impairment and frank dementia. The capability of antiretroviral medications to suppress HIV-1 RNA levels in CSF to undetectable levels is restricted by the relative inability of these medications to cross the BBB. Some patients with HIV infection continue to experience neurocognitive deterioration even after treatment has suppressed viral replication in the plasma.

Some studies suggest that viral escape in CSF occurs in up to 10% of asymptomatic HIV-infected patients. These findings are based on small studies and only large and long-term follow-up studies will clarify the importance of CNS penetration of antiretroviral drugs in the final prognosis of HAND.

Discordant resistance patterns in CSF and plasma from HIV-infected patients may limit the effectiveness of future antiretroviral regimens and affect the development of HIV-1-related neurocognitive disorders despite recent encouraging evidence on the effect of HAART on neurocognitive function.

**Conclusions**

Discordance between plasma and CSF levels of HIV-RNA may have an important bearing on neurological involvement in HIV-infected patients. Survival of drug-resistant viral strains in the CNS could alter the effectiveness or ART. This fact underlines the need for conducting larger studies to address these issues.

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