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The value of brain MRI associated with CSF viral load in a patient living with HIV with encephalitis and undetectable viremia

Intérêt de l'IRM cérébrale associée à la virorachie chez un patient vivant avec le VIH atteint d'encéphalite avec une virémie indétectable

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RÉSUMÉ

L'inflammation persistante du parenchyme cérébral chez les patients vivant avec le VIH sous traitement antirétroviral (ARV) peut être liée à une réplication résiduelle du virus au niveau du système nerveux central (SNC), malgré une charge virale indétectable dans le sang. Nous rapportons le cas d'un patient de 41 ans, suivi pour VIH depuis 6 ans, observant correctement son traitement (Ténofovir-Emtricitabine-Efavirenz), avec une charge virale plasmatique indétectable, mais présentant des troubles neurologiques progressifs. L'IRM cérébrale a révélé des hypersignaux temporaux et mésencéphaliques avec prise de contraste. L'analyse du LCR a détecté une virorachie (310 copies/ml) malgré une virémie indétectable. Un traitement empirique a été instauré, mais l'évolution a été rapidement défavorable, avec décès au 10e jour. Ce cas illustre l'intérêt crucial de coupler IRM cérébrale et ponction lombaire chez les patients VIH présentant de nouveaux signes neurologiques, même sous ART efficace.

ABSTRACT

Persistent inflammation of the brain parenchyma in people living with HIV (PLWH) under antiretroviral therapy (ART) may be due to residual viral replication in the central nervous system (CNS), despite an undetectable plasma viral load. We report the case of a 41-year-old HIV-positive patient, adherent to ART (Tenofovir-Emtricitabine-Efavirenz), with a previously undetectable viral load, who presented with progressive neurological symptoms. Brain MRI revealed hyperintense lesions in the temporal and mesencephalic regions with contrast enhancement. Cerebrospinal fluid (CSF) analysis showed detectable HIV RNA (310 copies/mL), while plasma HIV RNA remained undetectable. Empirical treatment was initiated, however the patient's condition deteriorated rapidly, leading to death on the 10th day of hospitalization. This case highlights the importance of combining brain MRI and lumbar puncture for thorough evaluation in HIV-infected patients presenting with new neurological signs, even under effective ART.

1. Introduction

Serious neurological complications related to HIV have declined significantly since the advent of effective antiretroviral treatment (ART). However neurological, and neurocognitive manifestations (the so-called 'HIV-associated neurocognitive disorders': HAND) remain relatively common among people living with HIV (PLWH), possibly related to chronic inflammation of the central nervous system (CNS) [1,2]. The exact contribution of HIV itself, as opposed to other comorbid or coexisting conditions, remains a subject of ongoing debate [3].

The CNS is infected early during the primary HIV infection and serves as a major viral reservoir during chronic infection. Inadequate penetration of certain regimens across the blood–brain barrier may permit low-level, localized viral replication within the CNS, and potentially select for resistance mutations [4]. Although this phenomenon is relatively rare, it may contribute to a subset of neurocognitive disorders in otherwise virologically suppressed individuals. Furthermore, comorbid conditions such as cardiovascular disease, substance use, and aging can also affect CNS functioning in PLWH [5].

Magnetic resonance imaging (MRI) of the brain, along with cerebrospinal fluid (CSF) analysis obtained via lumbar puncture (LP), are critical tools for evaluating neurological symptoms in HIV-infected individuals, particularly when plasma viremia is undetectable. These investigations can uncover intrathecal HIV replication, CNS inflammation, or opportunistic infections that might otherwise go unnoticed. Early detection of such abnormalities allows for timely modification of ART regimens and may improve neurological outcomes. Cerebrospinal fluid (CSF) viral escape has been described in patients on ART with sustained suppression of HIV RNA in plasma. This phenomenon refers to persistent or re-emergent HIV replication in the CNS compartment despite effective systemic viral control [4, 6]. In such cases, HIV RNA levels in CSF exceed those in plasma, sometimes by more than one log, or are independently elevated (>200 copies/mL) while plasma viremia remains <50 copies/mL [7]. Most clinical laboratories now use assays with quantification thresholds of approximately 20 copies/mL for both blood and CSF. As a consequence of this immune system function restoration, opportunistic diseases have now become rare in PLWH with access to effective ART and life expectancy approaches that of the general population [8].

The HIV viral load is typically measured by reverse transcription polymerase chain reaction (RT-PCR) and expressed in copies per milliliter. "Viremia" refers to HIV RNA in the blood, while "virorachia" refers to HIV RNA in the CSF. When viral loads in either compartment fall below the detection limit of the assay, they are termed "undetectable." Incomplete viral suppression, or CSF viral escape, occurs when the virus persists in the CSF despite effective ART and an undetectable plasma viral load, and is frequently associated with new or worsening neurological symptoms.

This case report describes an HIV-positive patient, adherent to ART and with an undetectable plasma viral load, who presented with subacute rhombencephalitis due to HIV viral escape in the CNS.

2. Observation

2.1 Patient information

We present the case of a 41-year-old male patient known to be HIV-positive for 6 years, receiving Tenofovir-Emtricitabine-Efavirenz, with good adherence and immuno-virological control.

2.2 Timelines

Two plasma viral load measurements performed in the previous 12 months were undetectable, and CD4+ T-cell count was 600/mm³ six months prior to admission.

2.3 Clinical findings

He presented with a subacute onset of fever, aphasia, left ptosis and left mydriasis associated with a confusional state.

2.4 Diagnostic assessment

A non-contrast CT scan performed upon admission revealed no evidence of acute lesions, mass effect, or intracranial hemorrhage. Due to the persistence and progression of neurological symptoms, a brain MRI was conducted 48 hours later. The MRI revealed hyperintense lesions on T2-weighted and FLAIR sequences, predominantly involving the left mid-temporal region, the left mesencephalon, and peri-mesencephalic white matter. These findings were non-specific but suggestive of an underlying inflammatory or infectious process. On T1-weighted post-contrast sequences following gadolinium administration, the affected regions exhibited patchy to nodular contrast enhancement, particularly in the peri-mesencephalic and mesial temporal areas, indicating blood-brain barrier disruption consistent with active inflammation or viral encephalitis. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping showed no areas of restricted diffusion, effectively ruling out acute ischemic events. Susceptibility-weighted imaging (SWI) did not

demonstrate any microhemorrhages or calcifications. Additionally, there was no evidence of leptomeningeal or dural enhancement (figure 1).

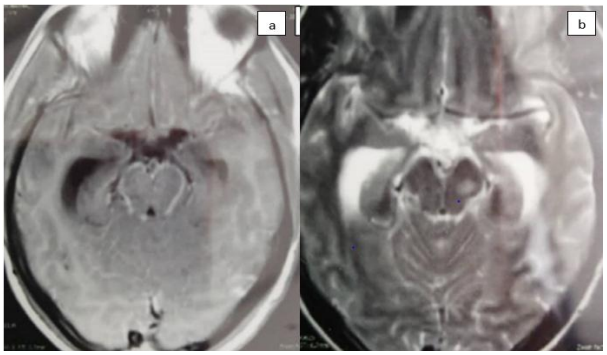

Figure 1: Cerebral MRI T1 peri-mesencephalic contrast enhancement (a) and left mesencephalic T Flair signal (b)

CSF analysis revealed 0.4 g / L of glucose, 0.6 g / L of protein without leukorachia. The CSF test for cytomegalovirus, Epstein-Barr virus, Herpes simplex 1 and 2, Acid-alcohol-resistant bacilli, varicella-zoster virus by PCR, syphilis, cryptococcosis and soluble Antigen were negative. However, we found the presence of HIV RNA in the CSF by RT-PCR revealed 310 copies / ml, for an undetectable viraemia (<30copies/ml). The CD4 + T cell count was 334 / mm3.

2.5 Therapeutic Intervention

Due to rapid clinical worsening, including progression of confusion, development of third nerve palsy (manifested as left ptosis and mydriasis), worsening aphasia, and appearance of pyramidal signs, empirical intravenous treatment with Acyclovir, Ceftriaxone, and corticosteroids was initiated.

2.6 Follow-up and Outcomes

A diagnosis of HIV-related rhombencephalitis due to CSF viral escape was made in the absence of alternative etiologies. The initial regimen: Tenofovir, Emtricitabine, and Efavirenz was planned to be switched to a combination with higher CNS penetration-effectiveness (CPE) score in accordance with available guidelines. The intended new regimen included Zidovudine, Lamivudine, and Dolutegravir, chosen for their improved CNS bioavailability. Unfortunately, the patient's clinical condition deteriorated rapidly, and he passed away on the 10th day of hospitalization, before the ART modification could be implemented.

3. Discussion

The mechanisms for HIV-induced neurological disease in treated patients can be explained by the limited diffusion of some ART through the blood–brain barrier and may allow HIV to persist and replicate at this level [9].

HIV infects the CNS early, that is, at the time of primary infection. The way the virus is transported there is still a matter of controversy. It could be transported by monocytes, lymphocytes or in the form of free viral particles [10]. The hypothesis of monocytes serving as "Trojan horses" is supported by the fact that the viral strains isolated from the CNS have a CCR5 tropism and replicate efficiently in cultured macrophages. After crossing the blood-brain barrier, HIV appears to primarily infect macrophages in the brain parenchyma (microglial cells). It is also capable, but to a lesser extent, of infecting astrocytes [11]. In contrast, neurons and oligodendrocytes are refractory to HIV infection. Replication of HIV in the CNS causes an inflammatory reaction characterized by the presence of numerous CD8 + T lymphocytes with release of pro-inflammatory mediators as well as reactive astrocytosis. This inflammatory reaction is characteristic of HIV encephalopathy, itself generally associated with cognitive impairment [12]. There does not appear to be a correlation between the severity of cognitive deficits and the HIV viral load in CSF [13]. This suggests the important role of the cerebral inflammatory response secondary to viral replication, regardless of the magnitude of the latter.

There are various clinical pictures associated with an escape of the HIV in the CNS, Clinical presentations are often subacute and may include meningitis, encephalitis, or myelitis. Among the symptoms and signs reported, some authors describe persistent headache, cerebellar dysfunction, pyramidal syndromes, cognitive impairments, and even altered levels of consciousness [14]. Our patient presented a progressive worsening of clinical picture in 5 days made of pyramidal syndrome, confusional syndrome and fever. The clinical vignette illustrates a virological escape at the level of the CNS. In India, Dravid et al. [15] found that out of the 1584 virologically suppressed individuals, 71 (4.4%) patients had neurologic symptoms during follow-up and required inpatient care. Twenty of 71 (28.2%) patients with neurologic clinical presentation had CSF/Plasma HIV-RNA discordance. Imbalance during walking, tremor of hands, and forgetfulness were the most common presenting symptoms of patients presenting with discordance. Twelve of 20 (60%) had subacute onset of symptoms. Canestri et al. [4] in his French series identified 11 chronically HIV-infected patients presenting with acute or subacute neurological

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symptoms, an active viral replication in CSF contrasting with suppressed plasma viremia, and a good immune status. Symptoms occurred subacutely in 8/11 patients, whereas the clinical presentation was acute in the remaining 3/11 patients. All patients were afebrile except 2 who had a low-grade fever (temperature < 38.5°C).
Faced with the clinical presentation of encephalic involvement in HIV-infected patient, an MRI was performed within 2 days of his admission in our hospital. The lesions found on imaging are those described in the literature: brain MRI reveals hyperintensities lesion in T2 and FLAIR at the level of the white substance. Most common MRI findings in patients with CSF/plasma HIV discordance in India series were generalized cerebral atrophy and asymmetrical, non-enhancing periventricular white matter hyperintensities on T2 and FLAIR images [15]. Three patients had HIV-related meningoencephalitis on MRI. Lesions tend to persist despite symptom resolution, lasting several months to several years [4, 14].

On the series of Dravid et al. median nadir CD4 count and median CD4 count at the time of discordance was 54.5 (IQR: 29.0–102.3) cells/mm3 and 352 (IQR: 200.3–505.8) cells/mm3, respectively [15]. Median plasma and CSF VL in patients with CSF/plasma HIV discordance was 120 (IQR: <20 to 332.5) and 4250 (IQR: 2550.0–9615.0) copies/mL, respectively. Abnormal CSF studies (high CSF protein, abnormal CSF glucose, or lymphocytic pleocytosis) were found in 18 of 20 (95.0%) patients. Median CSF protein was 97.5mg/dL (IQR: 80.25–107.75), median CSF sugar was 54mg/dL (IQR: 45.75–56.50), and median CSF cell count was 18cells/mm3 (IQR: 10.0–35.0). In order to estimate the brain penetration of ART, a score was published by Letendre et al. in 2008 and revised in 2010 (Tableau I) [16].

He presented the ART brain penetration efficiency score called CPE ranking system, established on the basis pharmacological studies at the CSF level, properties physicochemical of molecules and their efficiency in terms of suppressing virorachia.
In this system, ART are classified into four categories. The higher the score, the better the brain penetration of the drug. For combined treatment, the score of each molecule is added. High scores were associated with low virorachia as well as an upgrade cognitive functions in some Conversely, a low score was associated with an escape of HIV in the CSF [5, 14],[11]. Our patient had rather low CPE scores on 7, ART regimen took by our patient (Efavirenz, Tenofovir, Emcitricitabine) is the most frequently used ART regimen as describe by HIV causal collaboration [17] (Tableau II).

Tableau I: Revised central system penetration effectiveness ranking by letendre et al. [16]

	CPE score			
Antiretroviral drug class	4	3	2	1
Nucleoside reverse transcriptase inhibitors	Zidovudine	Abacavir Emcitricitabine	Didanosine Lamivudine Stavudine	Tenofovir Zalcitabine
Non-nucleoside reverse transcriptase inhibitors	Nevirapine	Delavirdine Efavirenz	Etravirine	
Protease inhibitors	Indinavir/r	Darunavir/r Fosamprenavir/r Indinavir Lopinavir/r	Atazanavir Atazanavir/r Fosamprenavir	Nelfinavir Ritonavir Saquinavir Saquinavir/r Tipranavir/r
Entry/fusion inhibitors		Maraviroc		Enfuvirtide
Integrase strand transfer inhibitors		Raltegravir		

CPE :CNS penetration effectiveness

Tableau II: Most frequently used cART regimens with a low, medium, and high CPE score,HIV-CAUSAL Collaboration, 1998-2013

Regimen	No. of initators	CPE score (category)
Efavirenz, Tenofovir, Emtricitabine	14,839	7 (low)
Nelfinavir, Zidovudine, Lamivudine	3,368	7 (low)
Lopinavir, Ritonavir, Tenofovir, Emtricitabine	3,342	7 (low)
Efavirenz, Zidovudine, Lamivudine	5,346	9 (medium)
Lopinavir, Ritonavir, Zidovudine, Lamivudine	3,823	9 (medium)
Efavirenz, Lamivudine, Abacavir	1,837	8 (medium)
Nevirapine, Zidovudine, Lamivudine	3,373	10 (high)
Indinavir, Ritonavir, Zidovudine, Lamivudine	757	10 (high)
Efavirenz, Zidovudine, Lamivudine, Abacavir	409	12 (high)

cART: combined antiretroviral therapy; CPE: CNS penetration-effectiveness.

The patient unfortunately died before his ART was changed. Vassalo et al. and Ellis et al. in their prospective studies investigating the effect of ART with a high CPE score on neurocognitive disorders associated with HIV have obtained discordant results [18]. While the first shows that patients receiving combined ART at a high CPE score were the most likely to be stable or improve their cognitive performance during the two years of follow-up, the second could not prove such a cause-and-effect relationship [18]. More Prospective studies

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involving more subjects, a standardized battery of adequate neuropsychological tests and prolonged follow-up are therefore necessary to assess the impact of the optimization of the penetration of ART according to the CPE score on the control of virorachia and improvement of neurological and cognitive disorders.

4. Conclusion

This case illustrates the critical role of brain MRI and lumbar puncture in diagnosing CNS complications in HIV-infected patients, even when plasma viral load is undetectable and ART adherence is confirmed. Early imaging and CSF analysis should be systematically considered in any new neurological presentation to detect intrathecal viral replication and guide appropriate therapeutic adjustments.

Competing interests

None of the authors have any conflict of interest to disclose.

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