Discordance Between Cerebral Spinal Fluid and Plasma HIV Replication in Patients with Neurological Symptoms Who Are Receiving Suppressive Antiretroviral Therapy

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Objective. We report data on 11 patients with neurological symptoms and human immunodeficiency virus (HIV) cerebrospinal fluid (CSF) viremia contrasting with suppressed plasma HIV RNA during receipt of combined antiretroviral therapy.

Design. We retrospectively identified instances of central nervous system (CNS) symptoms in patients who had been receiving stable combination antiretroviral therapy. Discordance between plasma and CSF HIV RNA levels was defined by any detectable CSF HIV RNA level >200 copies/mL while plasma levels were <50 copies/mL or by a CSF HIV RNA level that was ≥1 log greater than the plasma HIV RNA level.

Results. Eleven patients had experienced acute or subacute neurological symptoms. All but one patient had CSF pleocytosis and/or elevated protein levels. The median CSF HIV RNA level was 880 copies/mL (range, 558– 12,885 copies/mL). Patients had been receiving stable combination antiretroviral therapy for a median of 13 months (range, 10–32 months). Eight of 11 patients had a plasma HIV RNA level <50 copies/mL, and 3 had plasma HIV RNA blips with their CSF HIV RNA level >1 log higher than their plasma HIV RNA level. Resistance-associated mutations were detected in 7 of 8 CSF HIV RNA genotypic strains. The median number of resistance-associated mutations was 6 (range, 2–8) to nucleoside reverse-transcriptase inhibitors and 3 (range, 1–9) to protease inhibitors. One patient had a virus harboring nonnucleoside reverse-transcriptase inhibitor mutations. The median central nervous system penetration-effectiveness (CPE) rank was 2 (range, 1–3), and 5 patients had a CPE ≤1.5. After antiretroviral therapy optimization based on genotypes and CPE, all patients clinically improved, with normalization of CSF.

Conclusions. Despite successful suppression of plasma viremia with antiretroviral therapy, HIV may replicate in CSF, with development of CSF HIV resistance resulting in acute or subacute neurological manifestations.

Human immunodeficiency virus (HIV), in addition to its tropism for the immune system, shares with lentiviruses a tropism for both the central and peripheral nervous system [1, 2]. Acute and subacute neurological disorders related to HIV have been described through-out the natural evolution of HIV disease. These include acute meningitis, especially during primary infection [3]; myelitis; and chronic central nervous system (CNS) injury causing neurocognitive impairment, such as AIDS dementia complex [4].

In the pre–highly active antiretroviral therapy era, high HIV RNA levels in cerebrospinal fluid (CSF) were found to be associated with acute HIV encephalitis during primary infection [3], chronic HIV encephalitis, and AIDS dementia complex [5]. Since the advent of combined antiretroviral therapy (cART), several studies have shown the efficacy of cART in reducing CSF HIV RNA levels [6–10], which is associated with a neuro-psychological improvement [11–13]. In accordance

with this finding, the incidence of HIV-associated dementia significantly decreased from 5.9 cases per 100 person-years in 1994 to 0.5 cases per 100 person-years in 2002 [14].

Nevertheless, some recent studies have shown an increased prevalence of mild to moderate neurocognitive impairment [15, 16] causing an attenuated form of dementia that may continue to progress despite effective ART [16]. Furthermore, in some reports, despite suppression of viral replication in plasma during cART, persistent viremia was detected in the CNS [17, 18].

However, to our knowledge, only 1 instance of acute CNS symptoms has been reported in a patient receiving ART who had optimally suppressed plasma HIV RNA [19]. In this study, we highlight 11 cases of CNS disorders in patients chronically infected with HIV who had suppressed plasma HIV RNA viremia during cART.

METHODS

We retrospectively identified HIV-infected patients with neurological symptoms concomitantly with a CSF HIV RNA level >200 copies/mL contrasting with suppressed plasma viremia. This study was performed in infectious diseases departments at 2 university hospitals that attend to ~6000 HIV-infected patients per year. To be selected for the study, patients had to have received stable cART for a minimum of 6 months and to have a plasma HIV RNA level <50 copies/mL for at least 3 months before the neurological episode. Clinical manifestations were defined as the occurrence of acute (<2 weeks) or subacute (<4 weeks) neurological symptoms in patients with no history of HIV encephalitis. Patients with any psychiatric disease and/ or neurological involvement for any other reason were not included. The cognitive disorders were assessed using the Mini Mental State. All patients were evaluated by a neurologist at the time of their neurological symptoms. All patients had plasma HIV RNA assessed at the time of CSF HIV RNA level measurement. Plasma and CSF HIV RNA levels were quantified using Amplicor, version 1.5 (HIV Monitor Kit; Roche), with a detection limit of 50 copies/mL in plasma and 200 copies/mL in CSF. Blood $CD4^+$ T cell count measurement was performed using Facscount (Immunochemistry Systems; Becton Dickinson). Discordance between plasma and CSF HIV RNA levels was defined by any detectable CSF HIV RNA level >200 copies/ mL while plasma levels were <50 copies/mL or by a CSF HIV RNA level ≥1 log greater than the plasma level.

Genotypic viral resistance tests were performed in CSF or plasma samples when HIV RNA values were above the detection limit. Protease and reverse transcriptase genes were sequenced using an automated population-based full sequence analysis (ABI 3100 Genetic Analyser; PE Applied Biosystems). Antiretroviral drug concentrations in plasma and CSF were determined using high-performance liquid chromatography coupled with Photodiode array-ultraviolet or fluorimetric detection accord-

ing to previous published methods [20]. The time of the last drug intake and obtainment of samples was recorded for each measurement; antiretroviral drug concentration troughs were determined just before administration. The antiretroviral drug penetration scores in the CNS were estimated using the CNS penetration-effectiveness (CPE) ranks proposed by Letendre et al in the CHARTER Study [21]. Standard bacteriological and fungal cultures, including those for *Mycobacterium tuberculosis* and *Cryptococcus neoformans;* testing for antibodies against syphilis; and polymerase chain reaction assays for Epstein-Barr virus, cytomegalovirus, varicella zoster virus, herpes simplex virus, and John Cunningham virus were systematically performed. Descriptive statistics are presented as percentages or median value (range) for continuous variables.

RESULTS

From January 2004 through February 2009, we identified 11 chronically HIV-infected patients presenting with acute or subacute neurological symptoms, an active viral replication in CSF contrasting with suppressed plasma viremia, and a good immune status. Individual patient's characteristics are detailed in Table 1.

The patients comprised 7 men and 4 women with a median age of 50 years (range, 36–68 years). The median duration of HIV infection was 15 years (range, 5–20 years). The median duration of ART was 12 years (range, 7–20 years). At the time of the neurological episode, the patients' antiretroviral regimens had been unchanged for a median duration of 13 months (range, 10–32 months) and consisted of nucleoside analogue reverse-transcriptase inhibitors (NRTIs) plus protease inhibitors (PIs) boosted with ritonavir in 6 patients, NRTIs plus nonnucleoside analogue reverse-transcriptase inhibitors (NNRTIs) in 2 patients, boosted PI monotherapy in 2 patients, and an NRTI, a PI, and enfuvirtide in 1 patient (Table 1). The median duration of HIV RNA suppression in plasma was 18 months (range, 10–75 months). The median $CD4^+$ T cell count was 432 cells/mm^3 (range, 107–631 cells/mm^3). Eight patients had stage C HIV infection, according to the Centers for Disease Control and Prevention classification. The median nadir $CD4^+$ T cell count was 55 cells/mm^3 (range, 2–250 cells/mm^3). Six patients had chronic coinfection with hepatitis viruses: hepatitis C in 3 patients, hepatitis B in 2, and both hepatitis B and hepatitis C in 1. In the context of HIV infection, 4 patients had a neurological manifestation ≥5 years before the current episode; these included bacterial meningitis (in patient 10), cytomegalovirus retinitis (in patient 11), optic neuritis (in patient 4), and tuberculosis meningitis (in patient 5).

Clinical manifestations. Neurological symptoms are presented in Table 1. Symptoms occurred mostly subacutely in 8 patients, whereas the clinical presentation was acute in the remaining 3 patients. All patients were afebrile except 2 (patients

Table 1. Demographic Characteristics, Human Immunodeficiency Virus (HIV) Status, Neurological Presentation, and Virological Findings

Patient	Age, years	Nadir CD4+ T cell count, cells/mm³	CD4+ T cell count, cells/mm³	Time with plasma HIV RNA level <50 copies/mL, months	Neurological symptoms	Treatment	CSF HIV RNA level, copies/mL	CSF ART concentration trough, ng/mL	Plasma HIV RNA level, copies/mL	Plasma ART concentration trough, ng/mL	Resistance mutation detected in CSF	Change in treatment
1	50	250	592	36	Persistent headache	TDF FTC ATVr	12,885	12 NA <30	147	52 19 538	NRTI: M41L/E44D/D67N/L74V/M184V/210W/T215Y; NNRTI: none; PI: 36I	AZT, 3TC, IDVr
2	49	4	190	11	Memory disorders, cerebellar ataxia	AZT 3TC IDVr T20	845	28 201 154 <50	<50	<10 244 565 1427	NRTI: M41L/E44D/D67N/M184V/L210W T215Y; NNRTI: V179I; PI: L63P/V827/I85V	AZT, 3TC, IDV, LPVr, NVP
3	43	52	400	18	Cerebellar dysarthria, cerebellar ataxia	3TC ABC ATV IDVr	1190	NA 75 <30 97	<50	597 86 980 893	NRTI: M41L/D67N/T69D/L74V/M184V/L210W/T215F; NNRTI: L100I/K103N; PI: L10/I13/E35D/M36I/R41K/I54V/L63P/H69K/V82S	3TC, ABC, ATV, IDV, LPVr
4	50	221	432	68	Tactile allodynia	TDF FTC fAPVr	870	NA NA 47	78	NA NA 1495	NRTI: M41L/D67N/K70R/M184V/T215F/K219Q; NNRTI: none; PI: L10I/I62V/L63P	3TC, ABC, IDV, fAPVr
5	36	55	107	75	Glasgow Coma Score of 3	3TC ABC TDF DRVr	5035	<10 332 191 207	<50	<10 270 878 8992	NRTI: none; NNRTI: none; PI: none	Foscarnet, AZT, 3TC, ABC, TDF, LPVr, MRV
6	47	64	631	64	Persistent headache	DRVr	580	<5	<50	3522	NRTI: M184V/L74I; NNRTI: none; PI: none	3TC, ABC, DRV
7	44	211	544	14	Memory disorders, cerebellar ataxia, pyramidal syndrome	FTC ABC ATVr	558	NA NA 18	<50	NA NA 194	NA	FTC, ABC, EFV, fAPVr
8	53	25	360	12	Lower limb disesthesia and hypoesthesia	3TC AZT ABC EFV	1023	NA NA NA	<50	NA NA NA	NA	None
9	68	110	147	12	Memory disorders, left lower limb disesthesia	3TC DdI TDF NVP	586	NA NA NA	<50	388 NA 28 4864	NA	3TC, NVP, ATVr
10	68	25	534	18	Temporospatial disorientation, cerebellar ataxia	3TC AZT ATV	880	NA NA NA	<50	NA NA NA	NRTI: M41L/E44D/D67N/K70R/M184V/L210W/T215Y/K219Q; NNRTI: none; PI: I13V/L63P	3TC, AZT, fAPV, LPVr
11	55	2	593	10	Memory disorders, cerebellar dysarthria	LPVr	6999	NA	483	NA	NRTI: none; NNRTI: none; PI: M46V/I54V/L63P/V82A	3TC, ABC, EFV, LPVr

NOTE. ABC, abacavir; ATV, atazanavir; ATVr, atazanavir boosted with ritonavir; AZT, zidovudine; CSF, cerebrospinal fluid; DRVr, darunavir boosted with ritonavir; EFV, efavirenz; fAPV, fosamprenavir; fAPVr, fosamprenavir boosted with ritonavir; FTC, emtricitabine; IDV, indinavir; IDVr, indinavir boosted with ritonavir; LPV, lopinavir; LPVr, lopinavir boosted with ritonavir; MRV, maraviroc; NA, not available; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; TDF, tenofovir; 3TC, lamivudine; T20, enfuvirtide.

1 and 5) who had a low-grade fever (temperature, <38.5°C). Neurological symptoms were consistent with encephalitis, myelitis, and meningitis. The severity of the symptoms was variable from mild in 3 patients (patients 1, 4, and 6) to moderate in 2 (patients 8 and 9) and severe in 6 (patients 2, 3, 5, 7, 10, and 11). Two patients experienced only a persistent severe headache (patients 1 and 6). The others patients had several focal symptoms, including cerebellar involvement in 5 patients (patients 2, 3, 7, 10, and 11), pyramidal syndrome in 1 (patient 7), and myelitis in 2 (patients 4 and 8), which were associated in some patients with more-diffused symptoms, such as memory disorders (patients 2, 7, 9, and 11) and temporospatial disorientation (patient 10). The patient with the most severe symptoms (patient 5) presented with altered consciousness at admission to the hospital, where the patient was brought by a friend who found her unresponsive. Within 4 h after hospital admission, the patient was in a coma and was transferred to the intensive care unit for respiratory assistance. No toxic or substance abuse causes or epilepsy were found.

CSF parameters and MRI results. CSF cellularity and biochemical abnormalities were found in all but one patient. Overall, 10 of 11 patients had elevated protein CSF levels (median, 0.85 mg/dL; range, 0.45–3.64 mg/dL). CSF pleocytosis was observed in 8 of 11 patients (median white blood cell count, 31 cells/mL; range, 6–270 cells/mL; 90% lymphocytes; range, 80%–99%). No red blood cells were present in the CSF samples. All CSF samples were negative for bacteria, fungi, or other viruses. All patients had MRI abnormalities consisting of T2-weighted sequences showing white matter hyperintensities, suggestive of encephalitis in 9 patients and myelitis in 2 patients [22].

HIV RNA CSF and plasma parameters. Initial CSF evaluation showed that all patients had HIV replication in CSF with a median HIV RNA load of 880 copies/mL (range, 558–12,885 copies/mL). At the same time, patients had a plasma HIV RNA load <500 copies/mL, and 8 consistently had a plasma HIV RNA load <50 copies/mL. Three patients (patients 1, 4, and 11) had transiently detectable plasma HIV RNA levels (147, 78, and 483 copies/mL, respectively), but all 3 had a plasma HIV RNA level <50 copies/mL in the previous 6 months. For the 3 patients with detectable plasma HIV RNA, the CSF HIV RNA level was at least 1 log higher than the plasma HIV RNA level (12,885, 870, and 6999 copies/mL).

Determination of antiretroviral drug concentrations was done in 8 of 11 plasma samples and 7 of 11 CSF samples. In accordance with the interval between the last drug intake and obtainment of samples, all available plasma concentrations were within the adequate range (Table 1). The highest drug levels in CSF samples have been found for indinavir during concomitant administration of ritonavir and for abacavir and lamivudine. The CSF concentration was above the detection threshold for atazanavir and enfuvirtide.

Among the 11 patients, the CPE score was 1 for 3 patients (patients 1, 6, and 11), 1.5 for 2 patients (patients 4 and 9), 2 for 2 patients (patients 7 and 10), and 3 for 3 patients (patients 3, 5, and 8). Overall, 5 of 11 patients had a CPE score <2.

Results of genotype resistance tests for CSF HIV RNA were available for 8 of 11 patients (Table 1). The presence of resistance-associated mutations was found in 7 of 8 patients, with a median number of 6 resistance-associated mutations to NRTIs (range, 2–8) and 3 to PIs (range, 1–9). One patient had a virus harboring NNRTI mutations.

In 5 patients, the virus present in the CSF was not sensitive to the antiretroviral drugs present in their regimen. To compare plasma and CSF resistance profiles, a genotypic resistance test was performed for 2 of the 3 patients with plasma HIV RNA blips at the time of neurological symptoms (patients 1 and 11) that showed a similar resistance profile. Five patients had a plasma HIV RNA level <50 copies/mL and CSF HIV RNA harboring resistance-associated mutations (patients 2, 3, 5, 6, and 10). In patient 2, we found a genotypic resistance determination in a single sample with a detectable HIV load (431 copies/mL) 2 years previously that revealed a similar resistance mutation profile. Patient 6 experienced plasma HIV RNA replication 6 years previously without a genotypic resistance test. The 3 remaining patients (patients 3, 5, and 10) had complete suppression of plasma viral load since the initiation of ART.

EVOLUTION

ART was modified for 10 of 11 patients (Table 1), as follows: addition of a second PI ($n = 4$), modification of the current PI ($n = 3$), addition of 1 NRTI ($n = 2$), and addition of 3 new drugs ($n = 1$). In 7 patients in whom drug concentrations could be measured after treatment modification, all plasma values were in the expected range. The highest drug levels in the CSF were found for indinavir, nevirapine, abacavir, maraviroc, and lamivudine. After treatment modification, no patient had a CPE score <2: 1 had a CPE score of 2, 1 had a score of 2.5, and 6 had a score >3.

All patients improved clinically within 4 weeks, including patient 8, for whom treatment remained unchanged. The comatose patient was extubated 2 days later. The patient's neurological functions improved, but cerebellar syndrome continued to manifest. A median of 6 weeks (range, 2–16 weeks) after treatment modification, CSF samples were monitored in 9 of 11 patients and showed normalization of cellularity and protein level. All CSF HIV RNA values were below the level of detection of 200 copies/mL in all patients.

DISCUSSION

We describe here 11 patients presenting with neurological symptoms in an unusual clinical and virological context, given that all had a good immune status with suppressed HIV viremia.

We hypothesised that HIV RNA in the CSF was the cause of neurological symptoms for the following reasons. The CSF investigations performed in the presence of clinical symptoms showed an active viral replication in all patients and a meningeal inflammation in all except one patient. No other infectious etiology for these disorders could be found. Neuroradiological evaluations showed, in all cases, findings in favor of HIV CNS encephalitis or myelitis. Finally, in these neurologically symptomatic patients, the modification of ART selected to achieve better virological effect on CSF HIV RNA led to clinical improvement and subsequent control of CSF viral replication.

The clinical presentation of the cases described in our study was variable from a simple headache to coma with differing degrees of gravity. These cases, because of the rapidity of the symptomatology, appeared to resemble more closely the acute meningoencephalitis and myelitis usually reported in the context of primary infection or discontinuation of ART [23] with abrupt increase of viral replication in the CNS.

There are obviously limitations to our study. First, as for all retrospective studies, data are based on chart reviews, and complete neurological investigations may have been lacking. Second, because the explorations were driven by clinical findings, it was impossible to evaluate the prevalence of such CSF and plasma HIV RNA discordance among patients with suppressed HIV viremia and their potential neurological consequences. Indeed, if focal neurological symptoms as significant as ataxia or sudden coma lead to complete investigations, including CSF examinations, symptoms such as headaches or symptoms considered to be common in HIV-infected patients, such as paresthesias or dysethesia, may never lead to CSF viral investigation.

The most striking feature of this neurological entity is the discordance between the presence of viral replication in CSF and its control in plasma. Indeed, all patients had suppressed viremia for ∼18 months and relatively good immune status, with a median CD4+ T cell count >350 cells/mm³. To our knowledge, this observation of symptomatic patients with discordant CSF and plasma viral loads has not yet been reported. Some studies have reported persistent viral replication in postmortem brain tissue samples from patients with controlled plasma HIV RNA level [24, 25] or low HIV replication (2.5 copies/mL in the CSF) in asymptomatic patients receiving successful cART [17, 24, 25], suggesting local replication of HIV.

This can be evidenced by deep bifurcation in the phylogenetic trees of HIV strains between plasma and CSF that lead to clonal amplification and to compartmentalization of HIV infection in the CNS [26–28]. Of note, the determination of drug-resistance profiles in strains from 8 patients showed resistance-associated mutations in all strains except one. In 3 patients with prior virological failure, CSF HIV RNA resistance mutations might have originated from resistance developed in plasma HIV RNA.

However, in 3 other patients, the absence of any episode of virological failure since the start of ART suggests that resistance in the CSF HIV RNA was attributable to autonomous replication and independent evolution of drug resistance in the CSF.

Development of discordant resistance-associated mutations could also be explained by poor penetration through the blood-brain and blood-CSF barriers resulting in low concentrations in the CSF. The CHARTER Cohort group defined a CPE rank to characterize drug penetration in the CNS and the correlation with CSF HIV replication [21]. However, in our study, CSF HIV replication could be explained in only 5 patients by insufficient drug penetration in the CNS compartment, according to the CHARTER score. Two of the 11 patients were receiving monotherapy with a ritonavir-boosted PI (lopinavir and darunavir). In a recent open-label study involving 60 patients randomized to receive either lopinavir monotherapy or maintenance of triple-drug therapy, 3 patients had CSF samples with detectable HIV RNA during monotherapy [29]. Although these compounds have a reasonable penetration in the CSF, monotherapy may not be sufficient to control HIV replication in the CNS, especially in patients with a low nadir CD4+ T cell count. Of interest, all patients reported here except one had a nadir CD4+ T cell count <250 cells/mm³, suggesting a longer duration of viral replication, a lower immune status, and, therefore, a higher risk for the presence of HIV in the CNS.

In conclusion, physicians should be aware of the possibility of acute HIV-associated CNS disorders even in the presence of minor neurological complaints that should prompt a CSF evaluation with the determination of viral replication and genotypic resistance testing. There is a specific need for a better understanding of the dynamics of viral replication in the CNS compartment and its consequences on potential neurological dysfunctions.

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