International Journal of Infectious Diseases 84 (2019) 39–43

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Short Communication

Symptomatic HIV CNS viral escape among patients on effective cART

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ARTICLE INFO

Article history:
Received 23 January 2019
Received in revised form 18 March 2019
Accepted 28 March 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Symptomatic CNS escape
HIV viral escape CNS
Cerebral penetration effectiveness score
Cognitive decline HIV

ABSTRACT

Objective: The clinical syndrome in symptomatic HIV associated CNS viral escape is poorly defined. We attempted to describe the clinical syndrome, laboratory profile, radiological features and outcomes of HIV infected patients with symptomatic central nervous system (CNS) viral escape in our study.
Methods: This is a retrospective study were adult patients with HIV infection on cART admitted with a diagnosis of CD8 encephalitis or CNS viral escape in a large teaching hospital in South India was identified.
Results: The mean age of the eleven patients included in the study was 37.5 years. Most patients had received almost a decade of antiretroviral treatment at diagnosis (mean: 11.18 years). All patients presented with global cerebral syndrome. Cognitive decline, tremors, and headaches were common manifestations. All patients had lymphocytic pleocytosis (mean cell count: 44.63 cells/ml; lymphocyte percentage: 94.81%) with elevated protein (mean: 125.36 mg/dl). All patients were on boosted protease inhibitors (81.8% on Atazanavir and 18.18% Lopinavir). All except one patient was on Tenofovir and lamivudine combination therapy. White matter changes and deep brain nuclei involvement were common. Most patients required a change of cART to regimens with better CNS penetration and suppression of the resistant virus in the plasma and improved.
Conclusion: CNS viral escape should be considered as a differential among patients on Atazanavir presenting with non-focal cerebral syndrome and CSF lymphocytic pleocytosis.

Despite the improved survival and outcomes with combination antiretroviral therapy (cART) in HIV affected individuals, a significant number of patients fail first line cART (Aghokeng et al., 2014). Switching to a new nucleotide/nucleoside reverse transcriptase inhibitor (NRTI), continuing lamivudine and adding a ritonavir boosted protease inhibitor (PI) is the commonly used second line regimen as a part of public health approach (Consolidated ARV guidelines, 2013). Generic heat stable Lopinavir or Atazanavir boosted with Ritonavir are the most common PIs used in this setting in many developing countries. In contrast, in Europe and North-America darunavir or Integrase inhibitor-based regimens predominate.

Most cART have excellent CNS penetration and are very effective in suppressing HIV replication in the CNS (Staprans et al., 1999). cART has resulted in overall reduction in the burden of HIV associated neurocognitive decline (HAND) as well. Among patients on adherent effective ART, about 5–10% of patients have detectable HIV in the CSF despite a suppressed peripheral blood viral load and most of them are asymptomatic (Clifford, 2010; Edén et al., 2010). A small percentage of patients with CNS viral escape present with progressive acute or subacute neurological symptoms contributing to significant morbidity (Canestri et al., 2010). Long ART treatment, significant treatment interruptions and PI based therapies are associated with CNS viral escape. Many of these patients have evidence of

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https://doi.org/10.1016/j.ijid.2019.03.033

Table 1
Summary of clinical characteristics, imaging and laboratory findings and outcomes of patients included in the study.

Age	43	44	40	24	17	37	35	39	37	67	30
Duration of HIV diagnosis (years)	6	14	10	6	16	9	12	13	15	17	10
Duration of ART (years)	6	14	10	6	11	9	12	13	15	17	10
Current ART regimen, duration	Tenofovir, Lamivudine and Ritonavir boosted Lopinavir (4 months)	Raltegravir with Boosted Atazanavir for 1 year	Tenofovir, Lamivudine and Atazanavir with boosted ritonavir for 9 months	Tenofovir, Lamivudine and Atazanavir with boosted ritonavir for 3 years	Tenofovir, emtricitabine, Ataznavir with boosted ritonavir for 7 months	Tenofovir/ Lamivudine/ Boosted Atazanvir for 8 months	Tenofovir/ Lamivudine/ Boosted Atazanvir for 8 months	Tenofovir/ Lamivudine/ Boosted Atazanvir for 1.5 years	Tenofovir, Lamivudine and Ritonavir boosted Lopinavir (4 months)	Tenofovir/ Lamivudine/ Boosted Atazanvir for 7 years	Tenofovir/ Lamivudine Ritonavir boosted atazanavir for 3 years
CD4 count (cells/uL)	444	467	283	344	309	228	175	177	377	411	493
Plasma viral load in RNA copies/uL (CSF vitral laod in RNA copies/uL)	8215 (NA)	<40 (1077)	499 (4001)	5023 (NA)	2484 (28415)	437 (18,696)	1873 (45189)	<40 (115)	1016 (15430)	5654 (10154)	531 (7805)
Resistance testing	NA	CSF: NRTI mutations: D67N, T215C, K219E NNRTI mutations: K103N, G190A PI mutations: M46I	Plasma: NRTI mutations: A62V, K65R, K70T, M184I NNRTI mutations: V90I, K103N PI mutations: nil	NA	CSF: NRTI mutations: M41L, E44D, D67N, T69D, V75M, M184V, L210W, T215Y, K219E NNRTI mutations: K101P, G190A, Y318F PI mutations: nil	CSF: NRTI mutations: E44D, D67N, M184V, T215Y NNRTI mutations: K101E, G190A PI mutations: nil	CSF: NRTI mutations: D67N, K70R, M184V NNRTI mutations: Y181C PI mutations: I50L, V82A, G73S	NA	CSF: NRTI mutations: D67N, V75M, M184V, T215F NNRTI mutations: V181C, V108L, F227L PI mutations: I84V, L10F, K20T	Plasma and CSF: NRTI mutations: M41L,M184V, T215F, K219E NNRTI mutations: Y188L, A98G PI mutations: G73S	NA
Clinical symptoms	cognitive decline, tremors and urinary incontinence	cognitive decline, tremors and headache	cognitive decline, memory impairment and tremors	seizures, headache and tremors	Seizures, headache and tremors	Headache and vomiting	Cognitive decline, behavioural changes, walking difficulty	Tremulousness, altered sensorium and irrelevant speech	Tremulousness, altered sensorium and irrelevant speech	Altered behaviour, hyper sexuality, urinary incontinence	Headache and gait ataxia
Duration of symptoms	8 months	3 months	1 month	1 month	12 month	1 week	12 month	1 month	2 weeks	3 years	4 months
CSF cell count (cells/μl)	55 cells/uL,	80 cells/uL	10 cells/ uL,	60 cells/ uL,	44 cells/ uL	100 cells/ uL	12 cells/ uL	8 cells/ uL	30 cells/ uL	16 cells/ uL	76 cells/uL
Lymphocytes	99,%	95%	88%	97%	93%	99%	88%	98%	95%	94%	97%
Monocytes	1%	5%	12%	3%	7%	1%	8%	2%	5%	6%	2%
Neutrophils							4%				1%
CSF protein (mg/dl)	179	137	198	82.1	94	120	185	78	95	81	130
CSF CD8 %	54.7	60	57	69.3	66.1	NA	NA	NA	40.7%	NA	NA

Brain MRI	Symmetric hyperintensities in deep grey and white matter.	Swelling and hypertensity of deep grey matter and deep brain nuclei with perivascular enhancement	Diffuse cortical and subcortical atrophy with periventricular white matter hyperintensities	Hyperintensities in the deep nuclei, deep white matter and diffuse leptomeningeal enhancement	Asymmetric hyperintensities around the deep nuclei with perivascular enhancement	Diffuse cerebral oedema with diffuse meningeal enhancement	Diffuse hyperintensity involving the white matter in both cerebral hemispheres	Diffuse hyperintensity involving the white matter in both cerebral hemispheres	Diffuse hyperintensities involving the white and grey matter	Diffuse hyperintensity involving the white matter in both cerebral hemispheres	Diffuse hyperintensity involving the white matter in both cerebral hemispheres and basal ganglia
Brain biopsy	Confirmed CD 8 encephalitis	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Treatment	Steroids with continuation of ART	Steroids with change of ART to Dolutegravir with boosted Darunavir	Steroids with change of ART to Dolutegravir with boosted Darunavir along with Zidovudineand Lamivudinr	Steroids with continuation of ART	Changed ART regimen to Raltegravir with boosted atazanavir	Changed ART regimen to Tenofovir, Lamivudine with boosted Lopinavir; Steroids were also added	Was planned to change ART to Dolutegravir with boosted Darunavir; patient could not afford the same	Referred to Government ART program with steroids	Changed to Dolutegravir with boosted Darunavir along with Tenofovir and Lamivudinr	Changed ART regimen to Dolutegravir with boosted Darunavir along with Zidovudine and Lamivudinr	Planned for change of ART
Follow up Plasma viral load	Patient died	Undetectable	Undetectable	Not available	Undetectable	Not available	Not available	Not available	Undetectable	Undetectable	Awaited
Outcome	Death	Partial recovery	Complete recovery	Partial recovery	Complete recovery	Complete recovery	Did not improve	Partial improvement	Complete recovery	Complete recovery	Awaited

intrathecal inflammation like elevated CSF pleocytosis and neoptrin (Peluso et al., 2012). The MRI findings in these patients overlap those with HAND with significant white matter and deep nuclear involvement.

Multiple studies have shown poor central nervous system penetration and sub-therapeutic concentrations achieved within the CNS with Atazanavir (Peluso et al., 2012; Lahiri et al., 2016). While longitudinal studies have evaluated the relationship between viral escape and multiple cART regimens, the clinical syndrome of viral escape in the CNS associated with PIs have not been clearly characterized so far (Best et al., 2009; Mukerji et al., 2018). In this study we describe the clinical syndrome, laboratory profile, radiological features and outcomes of eleven patients on PI based regimens with features consistent with symptomatic central nervous system (CNS) viral escape from a tertiary care institution from South India.

All patients on cART who presented to the Infectious Diseases Department with neurological manifestations were screened for CNS viral escape after ruling out opportunistic infections and malignancies and eleven patients were identified between 2014 to 2018. Their clinical, laboratory and imaging details were reviewed from the hospital electronic database and summarized in Table 1. The mean age was 37.5 years (SD 12.71) and 63.6% were men. The mean duration of HIV diagnosis and cART at the time of presentation were 11.6 years and 11.18 years respectively. All patients presented with a global neurological syndrome without any lateralising signs or symptoms. The common clinical presentations included cognitive decline (60%), headache (40%), tremors (40%), altered sensorium (20%) and seizures (20%). None of the patients had neck stiffness or signs of meningeal irritation. The mean duration of PI based therapy before the onset of symptoms was19.8 months (SD 2 years). The mean duration of symptoms at presentation was 8.43 months (SD 10.54 months).

All patients had lymphocytic pleocytosis (mean cell count: 44.63 cells/ml; lymphocyte percentage: 94.81%) with elevated protein (mean: 125.36 mg/dl). CSF flow-cytometry done in six patients revealed a predominant CD8 cell population (median: 58.5%; Range 40.7–69.3%) with reversal of CD4 to CD8 ratio in all patients. The median CD4 count at diagnosis was 344 cells/μL (Range 177–467 cells/μL). The median plasma viral load was 1016 RNA copies/μL (Range undetectable to 8215 copies/μL). The median CSF viral load done in nine patients was 10,154 copies/μL. Detailed evaluation for opportunistic infections including CSF bacterial, fungal, mycobacterial cultures, Xpert MTB/Rif, cryptococcal antigen, polymerase chain reaction for HSV1, HSV2, CMV, JCV and VZV, and serum Venereal Diseases Research Laboratory test (VDRL) was negative in all patients. Of the seven patients who underwent viral resistance testing in the plasma or CSF, three had PI mutations and all had NRTI and NNRTI mutations. In one patient with a undetectable viral load in the plasma, PI mutations were present in the CSF suggesting an origin of the PI resistance in the CSF.

All patients were on boosted protease inhibitors (81.8% on Atazanavir and 18.18% Lopinavir). PI based cART is used in 9.8% of HIV infected patients in our Institutions (281 of 2860 patients). All except one patient was on Tenofovir and lamivudine combination therapy. All patients included in the study had failed cARTregimen with two NRTIs and one NRTI before they were initiated on boosted PI based regimen.

MRI brain revealed deep white matter hyperintensities (54.54%), deep brain nuclei involvement (36.36%), leptomeningeal enhancement (18.18%) and perivascular enhancement in deep brain nuclei (18.18%). Prominent atrophy and cerebral edema were present in 1 patient each. Brain biopsy showed perivascular infiltration of CD8 positive cells in one patient (Figure 1). Most patients required change of cART to regimens with better CNS

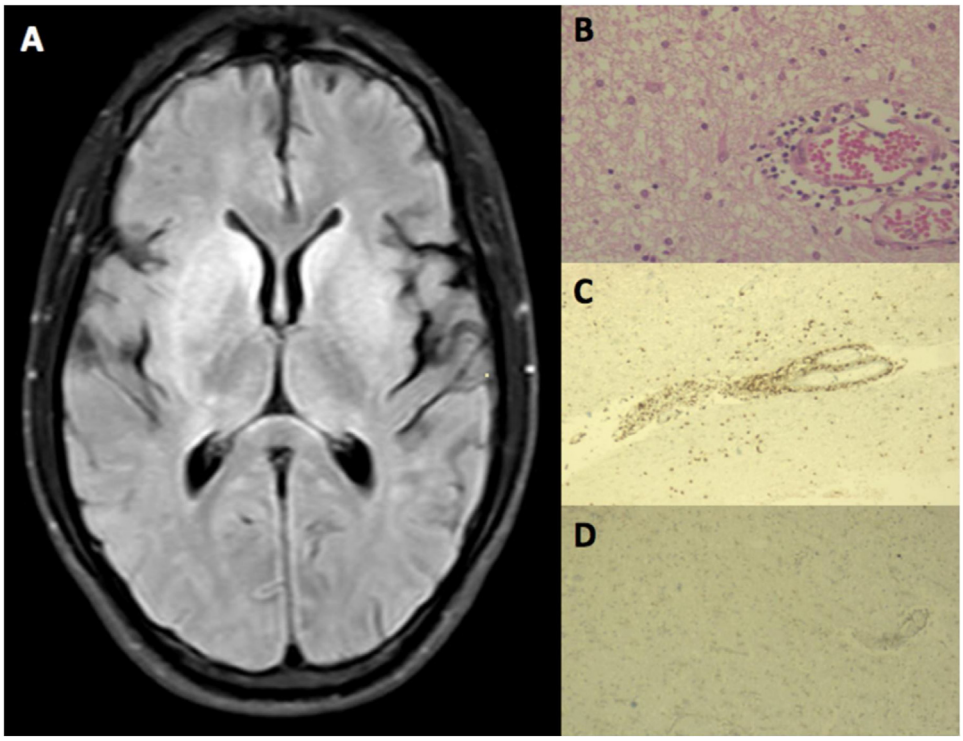

Figure 1. A. T2 Weighted FLAIR MRI images showing significant symmetric bilateral basal ganglia hyperintensities. B. Brain biopsy revealing intense perivascular inflammation with lymphocytes. C. Brain biopsy showing perivascular infiltration by CD 8 positive cells by immunostaining D. Brain biopsy showing paucity of CD4 immunostaining by the perivascular cells.

penetration and suppression of the resistant virus in the plasma. All five patients whose plasma viral loads were done after cART regimen change had undetectable virus. CSF follow up viral loads were not done in any of our patients.

Five patients made complete recovery, three had partial recovery, one did not improve and one died. One patient was lost to follow-up.

Symptomatic CNS viral escape should be ruled out in patients presenting with a global neurological syndrome while on cART. While NRTIs typically have excellent CNS penetration, Tenofovir achieves CSF levels below detection limits in most patients especially in the setting of concomitant Atazanavir. However, the most important parameter to decide TDF efficacy is the intracellular concentration of TDF within the brain tissue. Some early data from autopsy studies suggest that the brain tissue concentration of TDF may exceed that of CSF levels (Bumpus et al., 2015). In our study, all except one patient had TDF as the partner drug with Atazanavir. Also, as highlighted in our study, these patients are already exposed to NRTIs and likely have multiple NRTI mutations archived while started on second line ART. Less than optimal drug adherence also contributes and shortens the time to second line PI based ART failure (King et al., 2005). Also TDF causes reduction in the area under the curve concentrations and Cmin of Atazanavir when used in combination (Taburet et al., 2004). The combination may therefore be especially vulnerable regarding the CNS in combination with suboptimal adherence and resistance (Patel et al., 2018). Hence, it is likely that the factors compounding the poor CNS penetration of Atazanavir to induce viral escape are multifactorial and synergistic.

The clinical features and the imaging findings were suggestive of bilateral, symmetrical involvement of the brain. Tremors were suggestive of basal gangliar involvement as evidenced by perivascular enhancement in the deep brain nuclei noted in some patients. Also, effective treatment with newer drugs with better CNS penetration reversed the symptoms in many of our patients.

In 2013, Lescure et al described a novel entity, CD8 encephalitis in a series of 14 HIV infected patients with CD8 predominant encephalitis (Lescure et al., 2013). Most patients in this series have similar clinical and radiological features along with predominant CD8 cell population in CSF. In our patients, change of ART regimens including drugs with better CNS penetration was crucial to recovery and three patients who were initially treated only with steroids had relapse of symptoms with steroid discontinuation.

In summary, symptomatic viral escape should be considered as a differential diagnosis in patients presenting with global cerebral involvement while on TDF and ATV/R based cART.

We do not have any Conflict of Interest to disclose.

We have not obtained any funding for the study.

This study does not require an ethical committee clearance.

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