The symptomatology of cerebrospinal fluid HIV RNA escape: a large case-series

Description of Cerebrospinal Fluid HIV RNA Escape Symptomatology

Running title: CSF HIV RNA Escape Symptomatology

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Abstract:

Objective

To characterised the clinical, laboratory and radiological characteristics of persons with HIV (PWH) presenting with cerebrospinal fluid (CSF) HIV RNA escape.

Design

Retrospective case review of PWH presenting with symptomatic CSF HIV RNA escape at seven tertiary HIV clinical sites in UK and Italy

Method

PWH with symptomatic CSF HIV RNA escape episodes were identified and data obtained from medical records. CSF HIV RNA escape was defined as quantifiable CSF HIV RNA in unquantifiable plasma HIV RNA or CSF HIV RNA greater than plasma HIV RNA in cases where plasma HIV RNA was quantifiable. The duration of clinical symptoms was classified as acute (<2 weeks–6 months), or chronic (>6 months) and differences in presentation in those with CSF HIV RNA below and above 1000 copies/mL determined.

Results

We identified 106 PWH with CSF HIV RNA escape (65 male); 68 (64%) PWH had acute presentations and 38 (36%) had chronic presentations. Cognitive decline (n=54, 50.9%), delirium (n=20, 18.9%) and headache (n=28, 26.4%) were the most common presentations, with cognitive decline being more common in PWH who presented chronically compared with PWH who presented acutely (73.7% vs 35.3%, p=0.0002). Sixty PWH had CSF HIV RNA ≥1000

copies/mL and presented more frequently with confusion (n=15/60, 25.0%) compared to PWH with CSF HIV RNA <1000 copies/mL at presentation (n=5/46, 10.9%; p=0.03).

Conclusion

Cognitive decline, confusion and headache are the most frequent presenting symptoms of CSF HIV RNA escape and their relative frequency varied according to symptom onset and CSF HIV RNA concentration.

Keywords:

HIV; central nervous system; cerebrospinal fluid; Neurologic Signs and Symptoms; antiretroviral therapy

Introduction:

Modern combination antiretroviral therapy (ART) is highly efficacious at suppressing viral replication in both the plasma and central nervous system (CNS) compartments [1–3]. Rarely, however, HIV RNA is quantifiable in the cerebrospinal fluid (CSF) when not detectable in the plasma compartment or CSF HIV RNA is above the concentration quantified in plasma [4–6]. This entity is known as CSF HIV RNA escape.

Whilst there are several reviews on the prevalence and risk factors for CSF HIV RNA escape [7–9], data on symptomatology are lacking. Previous case series reported CSF HIV RNA escape were associated with new onset neurological symptoms, defined as 'symptomatic' CSF HIV RNA escape. The neurological presentations included gait ataxia, cognitive impairment, dizziness, fatigue and headache [7–9].

Here, our aim was to characterise the clinical characteristics of people living with HIV (PWH) presenting with symptomatic CSF HIV RNA escape. Secondly, we aimed to report the associated radiological and laboratory parameters.

Methods

Study setting and ethical considerations

We conducted a retrospective case review of PWH presenting with symptomatic CSF HIV RNA escape at seven tertiary HIV clinical sites (London (2), Milan (3), Turin (1), and Rome (1), (acknowledgements) between May 2003 and January 2019. All data were obtained from electronic clinical records, anonymised at site, and then collated centrally for analysis. For the London sites, additional patient consent and ethical approval were not required as per the UK National Research Ethics Service guidelines [10]. For the Italian sites, the study was approved

by the Ethical Committee of the participating Institutes and patients gave written permission for the use of clinical data (Local EC approval number 103/2015 for Turin, number for Milan and number for Rome).

Patient data collection and definitions:

PWH were required to be treated with ART for at least 6 months and have either new symptoms or significant progression of pre-existing neurological symptoms. Demographic, clinical and laboratory characteristics at diagnosis were recorded and included duration of known HIV-infection, clinical symptoms and duration, plasma and CSF HIV RNA concentrations, CSF characteristics, magnetic resonance imaging (MRI) (where available) and ART regimens. PWH who presented with a CNS infection and a concomitant rise in CSF HIV RNA were excluded due to the possibility of secondary CSF escape [6]. The duration of clinical symptoms were classified as acute/ subacute (<2 weeks–6 months), or chronic (>6 months). Plasma and CSF HIV RNA values were paired and performed within one week. A CSF HIV RNA cutoff of 1000 copies/mL was used when comparing the occurrence and type of symptoms as there was a similar proportion between the two groups above and below this cutoff.

Cognitive impairment was diagnosed by standard neurocognitive testing. Other symptoms are recorded as per initial review by physicians at presentation. Full clinical recovery was defined as resolution of symptoms after ART changes and partial clinical recovery was defined as objective improvement compared to initial presentation with residual symptoms on follow up review. Where available, reports of cerebral MRI with standard sequences reviewed by separate radiologists at different sites were included.

Laboratory methods:

CSF HIV RNA escape was defined as quantifiable CSF HIV RNA in the presence of unquantifiable plasma HIV RNA or CSF HIV RNA greater than plasma HIV RNA in cases where plasma HIV RNA was quantifiable [4,5,11]. For subjects with more than one episode of CSF HIV RNA escape, only the initial episode was included.

For the London sites, CSF and plasma HIV RNA were measured using the COBAS AmpliPrep/ COBAS TaqMan HIV-1 Test version 2.0 (Roche, Switzerland), with a lower limit of quantification of 40 copies/mL for the Royal London Hospital site, and 20 copies/mL for the St Mary's Hospital site. Sanger sequencing was used to sequence reverse transcriptase (RT) and protease (PR) genes for HIV resistance testing of CSF and plasma samples by ViroSeq (Abbott) or in-house method.

HIV-RNA was considered undetectable if <50 copies/mL (lower detection limit by the COBAS Amplicor HIV-1 Monitor assay, Roche, Basel, Switzerland) or <37 copies/mL [1-37] (lower quantification limit by Abbott Real Time HIV-1 m2000, Abbott Molecular Inc., Des Plaines, IL, USA) in Milan. For sites in Rome and Turin, the lower limit of HIV-RNA quantification by the Roche Amplicor assay v2.0 (Hoffman-La Roche, Basel, Switzerland) was 20 copies/mL.

Statistical Analysis:

Continuous variables were described using median and interquartile ranges and percentages were used to describe categorical data. Mann-Whitney U test and Fisher's test were used to compare continuous and categorical variables respectively. Univariate analysis was performed using logistic regression. Data manipulation and analysis was performed using RStudio, version 4.0.0 (RStudio, Boston, MA).

Results

Clinical Characteristics:

In 106 PWH (65 male, 41 female), median age was 51 years (IQR 47–56 years) and the median known duration of HIV-infection was 12 years (IQR, 6–13 years). ART data was available in 101 PWH at presentation, with boosted protease inhibitor (PI) containing regimes being most common (Table 1).

PWH with CSF HIV RNA escape presented with diverse clinical symptoms; 68 PWH had an acute presentation and 38 PWH had a chronic presentation. Cognitive decline (n=54, 50.9%), confusion (n=20, 18.9%) and headache (n=28, 26.4%) were the three most common presentations. Other presentations include extrapyramidal disease, seizures, personality changes, weakness, sensory and visual disturbances (Figure 1). Dystonia (n=1), and dysphagia (n=1) were also seen. Whilst not statistically significant, PWH who presented acutely frequently had headache (32.4% vs 15.8%, p=0.07) and confusion (20.6% vs 15.8%, p=0.61) when compared to PWH with a chronic presentation. PWH who presented chronically predominantly presented with cognitive decline compared with PWH with an acute presentation (73.7% vs 35.3%, p=0.0002) (Figure 1). The duration of HIV-infection had no significant influence on symptom occurrence in PWH within this cohort by univariate analysis.

Laboratory characteristics:

There were no significant differences in plasma or CSF laboratory characteristics between PWH with an acute presentation or chronic presentation (see Table, Supplemental Digital Content 1, illustrating the laboratory characteristics between PWH by symptom onset). Plasma HIV RNA was less than 1000 copies/mL in 82 (77.4%) PWH (undetectable in 46 (43.3%)), with a median of 68 copies/mL (IQR <40–858 copies/mL). Median CSF HIV RNA was 1500 copies/mL (IQR 314–16370 copies/mL) (Table 1). CSF pleocytosis (lymphocyte count >5 cells/mm^3) was observed in 64 PWH (60.4%). 84 (79.2%) PWH had a raised CSF protein >450 mg/L. All PWH had negative CSF bacterial cultures and viral PCR, including herpes virus 1, herpes virus 2, cytomegalovirus, varicella zoster virus and Enterovirus.

PWH with CSF HIV RNA >1000 copies/mL presented more frequently with confusion (n=15/60, 25.0%) compared to PWH with CSF HIV RNA <1000 copies/mL at presentation (n=5/46, 10.9%; p=0.03). PWH with confusion also had a higher CSF HIV RNA compared to PWH without confusion (11821 copies /mL (IQR 2027–76218 copies/mL) v 1174 copies/mL (IQR 220–9192 copies/mL), p=0.005). Other symptoms were not discriminative of the threshold.

Whilst plasma and CSF resistance testing was not possible in the majority of cases, paired analyses were performed in 40 PWH; nine PWH had mutations in CSF not detected on paired plasma samples. The M184V mutation in RT was the most frequent in plasma (n=23) and CSF (n=12). Seven PWH had wild type virus in both plasma and CSF samples. There was no significant difference in symptom occurrence or clinical course in PWH with or without the identifiable CSF resistant mutations.

Magnetic Resonance Imaging:

The majority of cerebral MRI reports of 95 subjects described diffuse white matter hyperintensities on T2-weighted sequences (n=74, 87.1%). Other abnormalities included atrophy (n=11, 12.9%) and scattered white matter foci suggestive of microvascular disease (n=5, 5.9%). Seven subjects with cognitive decline (n=3), headaches (n=2), tremors (n=2), and ataxia (n=1) had normal imaging on presentation.

Clinical management:

Data on ART changes to existing drug regimens on identification of CSF HIV RNA escape and clinical outcomes were available in 68 PWH, with 65 PWH having ART changes. Integrase strand transfer inhibitors was the most frequently added (n=38, 58.5%), with dolutegravir added in 14 cases.

After changes to ART regimens, 40 PWH (61.5%) had full clinical recovery and 7 PWH (6.6%) had partial recovery. Nine PWH with full recovery and five PWH with partial recovery had chronic presentations. 10 PWH showed no improvement, five PWH were lost to follow up, and another PWH experienced psychosis requiring admission to hospital. Two PWH died due to unrelated illnesses four months and a year later respectively after clinical recovery.

Three PWH did not have ART changes on CSF HIV RNA escape, all of whom had ongoing neurological symptoms but no further deterioration on follow up review.

Discussion:

We describe 106 PWH presenting with CSF HIV RNA escape with new or evolving neurological symptoms and signs. To the best of our knowledge, this study is one of the largest case series describing this rare entity. The neurological presentations we observed were varied at the time of presentation, but several symptoms were observed frequently. Confusion, headache, and cognitive decline were frequent in PWH with CSF HIV RNA escape, especially in those presenting acutely. This is consistent with findings reported in other studies [7–9]. Of interest, we observed new onset or worsening of seizures presentation, which to our knowledge has only been reported in two isolated case reports and one other case series [12–14].

While the pathophysiology of CSF HIV RNA escape is unclear, we hypothesise that symptoms are caused by a small but persistent replicating reservoir within the CNS compartment leading to inflammation. This is supported by the presence of CSF pleocytosis, diffuse white matter hyperintensities on MRI imaging and raised CSF protein levels. It potentially explains why some PWH presented chronically with deteriorated cognition. As the CNS viral reservoir increases, inflammation would increase and clinical symptoms would worsen, manifesting as confusion as seen in PWH with CSF HIV RNA of >1000 copies/mL.

Our case series highlights the importance of cerebral MRI in the management of PWH with new onset neurological symptoms where in almost all cases, abnormalities on cerebral MRI were evident. Encephalitis-like but non-specific hyperintense white matter changes seen on T2-weighted imaging were frequently observed, suggesting an underlying inflammatory process. Not all abnormalities would be HIV-related given the prevalence of non-infectious co-morbidities

in PWH [15]. However, such imaging reports may guide the clinical management of PWH presenting with new or worsening neurological complaints

We could not determine the underlying mechanisms of CSF HIV RNA escape within this cohort. Of note, a large proportion of the PWH in our report were on a PI-based ART regimen at the time of presentation. Some of the PI agents are reported to have CSF concentrations below the IC50 (e.g. atazanavir [16]), which may permit ongoing viral replication within the CNS compartment and manifest as CSF HIV RNA escape. However, pre-existing characteristics which motivate the use of PI based regimen are probable confounding risk factors: PI based ART regimens are prescribed due to previous HIV-drug resistance, poor adherence, or intolerance. These confounding factors may also explain the underlying mechanisms for CSF HIV RNA escape.

Our report is limited by the retrospective nature of a case series. Our observations are restricted to PWH undergoing investigations for new onset neurological symptomatology and cases could have been missed as PWH with milder neurological symptoms may not be identified. In addition, data on medication adherence and follow up data on CSF escape persistence is unavailable in PWH within this study.

Our report contributes to the recognition of CSF HIV RNA escape in the ART era and specifically adds to our understanding on the clinical presentation of this relatively rare, yet important entity in a large case series. Due to the varied neurological signs and symptoms of CSF HIV RNA escape, clinicians should be vigilant and assess HIV RNA in the CSF in PWH who present with a new onset neurological syndrome, in line with current guidelines [4].

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T.C contributed in data collection, data analysis, and wrote the manuscript.

V.D.Z contributed in study conception and data collection

A.G contributed in data collection and edited the manuscript.

J.A contributed in data analysis and edited the manuscript

S.G contributed in study conception, data collection and data analysis

A.A contributed in study conception and data collection

A.A.M contributed in study conception and data collection

A.S contributed in study conception and data collection

M.T contributed in study conception and data collection

A.E contributed in study conception and data collection

S.R contributed in study conception, data collection, data analysis and edited the manuscript

M.M contributed in study conception, data collection, data analysis and edited the manuscript

A.C contributed in study conception, data collection, data analysis and edited the manuscript

P.C contributed in study conception, data collection, data analysis and edited the manuscript

A.W contributed in study conception, data collection, data analysis and edited the manuscript

Conflict of Interest

JA has received support to attend scientific conferences from MSD and Gilead Sciences. AC has received honoraria from Gilead, Insmed, Janssen-Cilag, MSD, Viiv and he is currently receiving research grants from Gilead and Viiv. AW has been an investigator on studies, received research grants or honoraria from Gilead Sciences, ViiV Healthcare, MSD and Janssen. All other authors report no conflict of interest

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Figures and Tables:

Table 1: Subject demographic and laboratory characteristics at the time of diagnosis (n = 106)

Baseline Characteristics	
Age – years	51 (47-56)
Male – n (%)	65 (61.3)
Time since first positive HIV test – months	144 (75.5-212.5)
ART characteristics (n = 101):	
Triple Therapy – n (%)	
2 NRTI + PI/r	57 (53.8)
2 NRTI + NNRTI	9 (8.5)
2 NRTI + INSTI	2 (1.9)
3 NRTI	1 (0.9)
NRTI + PI/r + MVC	1 (0.9)
PI/r + INSTI + MVC	2 (1.9)
PI/r + INSTI + NNRTI	1 (0.9)
Dual Therapy – n (%)	
PI/r + INSTI	6 (5.7)
PI/r + MVC	3 (12.8)
INSTI + MVC	1 (0.9)
1 NRTI + PI/r	1 (0.9)
PI/r Monotherapy – n (%)	9 (8.5)
Quadruple therapy – n (%)	6 (5.7)
Quintuple therapy – n (%)	1 (0.9)
HIV parameters	
CD4 count (cells/μL)	363 (276-619)
Nadir CD4 count (cells/μL)	100 (30-193)
CD4 count <200 cells/μL at presentation – n (%)	19 (17.9)
Plasma HIV RNA	
Undetectable (<50 copies/mL)	28 (26.4)
Plasma HIV RNA if detectable (copies/mL) (*n*=78)	193 (44 -1717)
CSF laboratory characteristics	
CSF HIV RNA (copies/mL)	1500 (314-16370)
CSF white cells (cells/μL)	11 (3 – 22)
CSF protein (g/L)	0.71 (0.50-1.06)
CSF glucose (mmol/L)	3.2 (3.0-3.5)

Footnotes: Percentages were used to describe categorised data. Median and interquartile range (IQR) were used to report continuous data. NRTI, nucleotide / nucleoside reverse-transcriptase inhibitors; NNRTI, non-nucleoside reverse-transcriptase inhibitors; INSTI, *integrase* strand transfer *inhibitors; PI/r, ritonavir boosted protease inhibitor, MRV, maraviroc*

Figure 1: Bar charts showing symptom occurrence between PWH with acute and chronic presentation