HIV encephalitis following interruption of antiretroviral therapy: a case series

Singh S[1], Shaw S[2], Churchill D[2], Kulasegaram R[1], Holmes P[3], Dosekun O[2]

[1]Harrison Wing, Guy's & St Thomas' NHS Trust, London [2] Lawson Unit, Royal Sussex County Hospital, Brighton
[3] Dept of Neurology, Guy's & St Thomas' NHS Trust, London

Background

HIV encephalitis (HIVe) is well described in the context of primary HIV infection. However, there are also case reports of acute neurological impairment associated with HIV replication in cerebrospinal fluid [1,2] (CSF) despite good immune status and suppressed viraemia in plasma.

We present 5 cases of chronically HIV-infected patients who presented with signs and symptoms of acute encephalitis following interruption of antiretroviral therapy (ART).

Methods

Patients were retrospectively identified from cohorts at 2 large teaching hospitals (Guy's & St Thomas' Hospital, London and Royal Sussex County Hospital, Brighton) with attendances between 2010 and 2012.

Patients who fulfilled the following criteria were included in the analysis:

- Known to be infected with HIV for > 6 months
- On ART >6 months
- Presenting with neurological signs consistent with acute encephalitis for which no alternative cause could be identified

Data was collected from electronic patient records and case notes, then collated and analysed in an Excel spreadsheet.

Results

Patient demographics

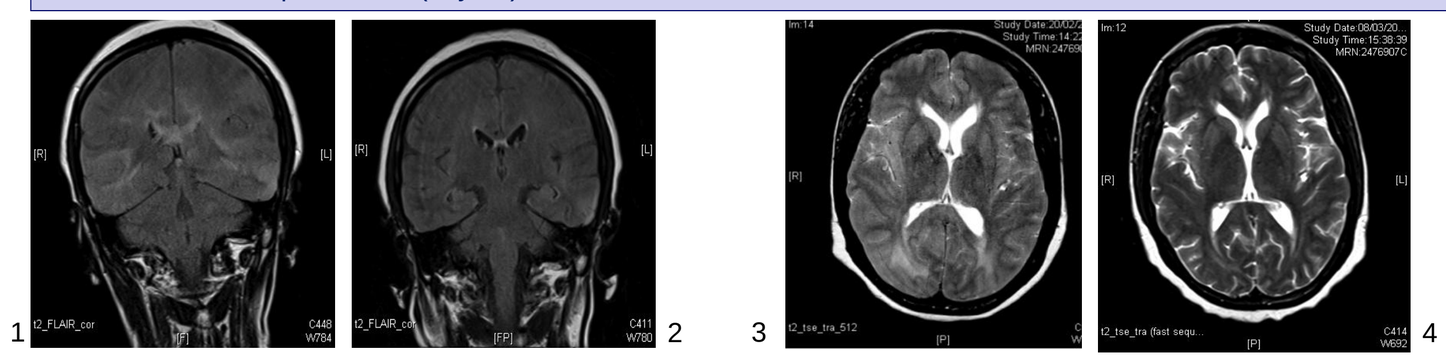
- 5 patients were identified: 3 males and 2 females.
- Mean age was 38 years (range 30-46)
- 2 patients were Black African, 2 White British and one White European

HIV indices

- 3 of the 5 patients (60%) had a records of plasma viral loads of <50 copies/ml prior to presentation. Prior CD4 and VL data were not available for one patient (Pt 1).
- All had discontinued their ART 2-12 weeks prior to admission
- Mean CD4 count was 625 cells/μL (range 144-1353)

Clinical features and investigations

- Presenting features included fever (n=3, 60%), confusion (n=3, 60%), vomiting (n=3, 60%), headache (n=3, 60%), ataxia (n=3, 60%), labile mood (n=2, 40%).
- Magnetic resonance imaging (MRI) showed extensive high-signal white matter changes in all cases. In addition, patient 1 had a further MRI 1 week following commencement of treatment which showed evidence of cerebral oedema with tonsillar herniation.
- In 4 cases where lumbar puncture was not contraindicated, there was evidence of CSF lymphocytosis (20 – 168 cells/mm3) and elevated CSF protein (0.74 – 5.5g/l).
- CSF analysis was negative for other pathogens, and there was no evidence of lymphoma.
- Empirical treatment with antibiotics and high dose aciclovir was administered, and ART restarted in all cases. One patient (pt 1) received high dose intravenous steroids in addition to the above.
- HIV viral loads in CSF were over 1 log greater than plasma HIV viral loads (mean 1.63, range 1.21 to 2.51).
- Symptoms and physical signs resolved within a mean of 25 days (range 15 – 32).
- CSF analysis was repeated in 4 cases and showed improvement of all? CSF parameters (day 4 – 20 after recommencing cART).
- 4 patients had repeat MRI 6-14 days following treatment: 3 showed progression of previously described changes, whilst 1 showed improvement (day 14).



MRI scans **1** and **3** on admission showing generalised oedema and high signal white matter change. Scans **2** and **4** post treatment showing resolution of these changes and reduction of oedema

Table: Patient demographics, HIV indices, clinical features and results

Patient	1	2	3	4	5
Sex/Age (yrs)	F/38	M/42	M/30	F/35	M/46
Ethnicity	Black African	Black African	White European	White British	White British
Last CD4 count (%)	144 (11%)	430 (25%)	674 (28%)	525 (40%)	1353 (42%)
Prior viral suppression <50 c/ml	No data	Yes	No (never <400)	Yes	Yes
Last ART regimen	Unclear (prescribed abroad)	Kivexa, atazanavir, ritonavir	Tenofovir, abacavir, atazanavir, ritonavir	Tenofovir, atazanavir, fosamprenavir, ritonavir	Darunavir, ritonavir (monotherapy)
Previous adherence	Poor	Poor	Poor	Good	Good
Presenting signs/symptoms	Headaches, confusion, vomiting, signs of raised intracranial pressure	Fever, vertigo, headache, vomiting.	Vomiting, vertigo, tinnitus, headache, ataxia, nystagmus, dysdiadokinesia, past pointing	Ataxia, confusion, febrile, labile mood	Ataxia, confusion, febrile, labile mood
CNS imaging	CT - paucity of sulci over cerebral vertex. MRI - widespread high signal change in deep white and grey matter. Mild generalised cerebral swelling	CT - NAD MRI - widespread high signal change in deep white matter consistent with acute encephalitic process. No oedema	CT NAD MRI - patchy high signal changes in deep white matter suggestive of acute encephalitic process. Mild local swelling.	MRI - global oedematous white matter change with brainstem and cervical spine involvement. Suggestive of encephalitic process ?immune mediated	MRI - non specific white matter foci, one of which enhances, and more diffuse signal change in frontal white matter without mass effect
CSF cell count	Lumbar puncture contraindicated	WCC 55 (100% lymphocytes)	WCC 168 (95% lymphocytes 5% polymorphs)	WCC 20 (mostly monocytes)	WCC 43 (98% lymphocytes)
CSF protein (g/L)	Lumbar puncture contraindicated	0.74	5.5	1.47	0.79
Plasma HIV viral load (copies/ml) on admission	790 (2.90 log)	3509 (3.55 log)	7358 (3.87 log)	420 (2.62 log)	147 (2.17 log)
CSF HIV viral load (copies/ml) on admission	Lumbar puncture contraindicated	57680 (4.76 log)	2100000 (6.38 log)	14577 (4.15 log)	2699 (3.43 log)
Other CSF findings	Lumbar puncture contraindicated	NAD	NAD	Oligoclonal bands in CSF	NAD
Treatment administered	Aciclovir, ceftriaxone. dexamethasone, combivir, maraviroc, atazanavir, ritonavir.	Aciclovir, ceftriaxone. Kivexa, darunavir, ritonavir	Aciclovir, ceftriaxone. Truvada, darunavir, ritonavir, maraviroc (subsequently altered to Lopinavir/ritonavir due to acute transaminitis)	Aciclovir, ceftriaxone. Truvada, darunavir, ritonavir, raltegravir	Aciclovir, ceftriaxone, combivir, darunavir, ritonavir
Follow up imaging	MRI at 1 week (after clinical deterioration) - evidence of tonsillar herniation. New areas of high signal change. MRI at 3 months - complete resolution of high signal changes. Reduction in cerebral oedema	MRI at 2 weeks - progression of changes. MRI at 5 months - marked improvement	MRI at 2 weeks - improvement of previously seen changes	MRI at 2 weeks shows progression	MRI at 6 weeks shows improvement
Repeat viral loads in CSF/plasma (copies/ml)	Day 4 CSF 31070 (4.49 log) plasma not done	Not repeated	Day 20 - CSF 2143 (3.33 log) Plasma 336 (2.53 log)	Day 18 CSF <40 Plasma <40	Month 4 CSF 402 (2.60 log) Plasma <40
Tlme to resolution of symptoms (days)	21	15	28	32 (discharged with residual ataxia)	29
Residual impairment	Relapsed with similar presentation after further treatment interruption	None	None	Mild ataxia. Emotional lability (likely premorbid)	None

Discussion

- Withdrawal of ART can lead to an acute encephalitis associated with rebound plasma viraemia, regardless of immune status. The diagnosis of HIVe is one of exclusion, and assessment includes neuroradiological examination and paired plasma and CSF HIV viral loads.
- There is some evidence that ART tailored to increase CNS penetration might be beneficial[1,2]. In our cases, all patients had their ART regimens modified, in some cases to include zidovudine, maraviroc and/or raltegravir.
- Cases of an acute and often fatal encephalitic process have been reported in patients with stable CD4 counts[3]. In some cases this process was thought to be related to ART interruption, with similarities in the presentation and MRI findings to patients in our series. Some also underwent brain biopsy which showed extensive CD8+ T cell infiltration. A fatal CD8+ T cell encephalitis has also been described in an autopsy study[4], which included 2 patients who presented having stopped ART. None of the patients in our series underwent brain biopsy.
- The cases we present highlight the possibility of HIVe in patients with intermittent adherence to ART, although the numbers are low. Clinicians should be vigilant about the risks of HIVe in intermittently adherent individuals, and consider including this in discussions about adherence to ART.

References

1. Wendel KA, McArthur JC. Acute meningoencephalitis in chronic human immunodeficiency virus (HIV) infection: putative central nervous system escape of HIV replication. *Clin Infect Dis* 2003;37:1107–11.
2. Bingham R et al. HIV encephalitis despite suppressed viraemia: a case of compartmentalized viral escape. Int J STD AIDS 2011 Oct;22(10):608-9.
3. Lescure FX, Amiel C, Gray F, et al. Lymphocytes T8 infiltrative encephalitis: a new form of neurological complication in HIV infection. XVIII International AIDS Conference. 2010. Vienna. Abstract WEAB0303.
4. Lucas S, Wong KT, Mahadeva U. Fatal CD8+ T Cell Encephalitis: An Observational Autopsy Study of an Emerging Complication in HIV-1-infected African Patients on Effective Long-term ART. 2011. 18th Conference on Retroviruses and Opportunistic Infections. Poster 398