

# HIV – Old Foe with a New Face

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## Abstract

We report a case of a middle aged seropositive male, virologically well suppressed on second line ART (Anti-Retroviral therapy) who presented with a subacute history of neurological symptoms. On imaging and CSF (cerebrospinal fluid) evaluation, he was found to have CD8 encephalitis - a new, rare but treatable entity. To the best of our knowledge, no case has been reported from India.

## Introduction

Spectrum of HAND (HIV-associated Neurocognitive disorders) varies from asymptomatic neurocognitive impairment to Minor neurocognitive dysfunction to HIV-associated dementia. It is the most common CNS complication of HIV.<sup>1</sup> CD8 encephalitis is a new form of CNS immune reconstitution inflammatory syndrome (IRIS)<sup>2</sup> characterized by CD8<sup>+</sup> T-cell infiltration into the brain without high viral burden in the CNS or typical IRIS presentation.<sup>3</sup> CD8 cells in CSF and post-gadolinium T1 perivascular contrast enhancement are diagnostic.<sup>4</sup> Very few cases have been reported.<sup>2-4</sup>

## Case

A 55 year old right handed businessman, known case of retroviral disease presented to us in July 2014 with a three month history of increased sleepiness, episodic involuntary facial movements, memory disturbance and slurring of speech. He was diagnosed

**Table 1: Serial CD4 and viral load in last ten years. Note the change of ART regimen to second line in 2009 (c) and stable CD4 and viral load at time of admission (h).**

| Year (ART regimen) : CD4 count ; Viral load (copies per ml)                       |
|---|
| 1 / 2004 (AZT <sup>†</sup> / 3TC <sup>‡</sup> / NVP <sup>§</sup> ) : 156 ; 60,000 |
| 1 / 2005 (AZT <sup>†</sup> / 3TC <sup>‡</sup> / NVP <sup>§</sup> ) : 540 ; <20    |
| 1 / 2009 { TDF <sup>  </sup> / FTC <sup>¶</sup> / ATV(r) ** } : 67 ; 740,000      |
| 1 / 2010 { TDF <sup>  </sup> / FTC <sup>¶</sup> / ATV(r) ** } : 474 ; <20         |
| 1 / 2011 { TDF <sup>  </sup> / FTC <sup>¶</sup> / ATV(r) ** } : 445 ; <20         |
| 1 / 2012 { TDF <sup>  </sup> / FTC <sup>¶</sup> / ATV(r) ** } : 400 ; <20         |
| 1 / 2013 { TDF <sup>  </sup> / FTC <sup>¶</sup> / ATV(r) ** } : 650 ; <20         |
| 7 / 2014 { TDF <sup>  </sup> / FTC <sup>¶</sup> / ATV(r) ** } : 525 ; 200         |

Abbreviations: † Zidovudine, ‡ Lamivudine, § Nevirapine, || Tenofovir, ¶ Emtricitabine, \*\* Atazanavir boosted with ritonavir

HIV-1 ten years back and started on an AZT/3TC/NVP regimen (Zidovudine, Lamivudine,

Nevirapine). Four years later, he developed Pneumocystis-Carinii pneumonia wherein his CD4 counts decreased >50% and viral load increased to >7,00,000 copies per ml.

Hence, he was shifted to second line ART - TDF/FTC/ATV(r) (Tenofovir, Emtricitabine, Boosted Atazanavir). He was virologically well suppressed on the second regimen for five years.

On admission, his Mini Mental Status Examination (MMSE) score was 19 with impaired recall and calculation. CNS examination revealed a bilateral upper motor neuron facial nerve involvement, prominent jaw jerk, grade four power in all limbs with spasticity, hyperreflexia, bilateral ankle clonus and bilateral Babinski's sign. The patient had spastic dysarthria with

**Table 2: Routine investigations on admission**

Investigations (Normal values with conventional units) : Values

- Haemoglobin (14 – 17.5 g / dL) : 13.0
- Leucocyte count (4.4 – 11.3 \* 10<sup>3</sup> / mm<sup>3</sup>) : 10.8
- Platelet count (172 – 450 \* 10<sup>3</sup> / mm<sup>3</sup>) : 350
- Serum creatinine (0.6 – 1.2 mg / dL) : 0.9
- Serum Na<sup>+</sup> / K<sup>+</sup> (mEq / L) : 135 / 3.5
- AST<sup>†</sup> (12 – 38 U / L) : 45
- ALT<sup>‡</sup> (7 – 41 U / L) : 20
- Serum bilirubin (0.3 – 1.3 mg / dl) : 2.7 (Indirect bilirubin – 2.4)
- Fundus examination : Normal

Abbreviations: † Serum glutamate oxaloacetate transaminase, ‡ serum glutamate pyruvate transaminase.

intermittent facial tics.

He was investigated as shown in tables and figures below. In view of MRI findings and stable CD4 count, special CSF investigations were done as in Table 4. Investigations revealed a significantly elevated CD8 cell count in CSF along with elevated CNS HIV viral load in the presence of suppressed plasma viral load. CNS immune dysregulation was thus evidenced by the disproportionate presence of CD8 cells in the CSF. Hence, he was given intravenous pulse methylprednisolone 500 mg for five days and ART regimen changed to ABC/3TC/DRV(r) (Abacavir, Lamivudine, Boosted Darunavir) to improve CNS penetration. His facial tics and drowsiness improved within two weeks followed by gradual improvement in memory (MMSE – 26) and spasticity over next eight weeks. At 1 year follow-up, he is stable without any neurological deterioration.

## Discussion

CD8 encephalitis is characterized by a massively diffuse but predominantly perivascular infiltration of polyclonal CD8<sup>+</sup> lymphocytes. Four causes have been identified: trivial infection in well controlled patients, CNS IRIS, virological escape and HAART interruption. There is a transient disequilibrium between HIV and brain immunity evidenced by the presence of numerous perivascular CD8 lymphocytes, reactive astrocytosis and microglial activation. The inconstant and weak HIV-1 p24 antigen immunostaining on brain biopsies confirmed that microglial activation was not due to underlying viral replication.<sup>3</sup>

Mascolini's group of fourteen HIV patients had a median age of 41, HIV infection for 10 years duration, median CD4 - 493 and median plasma viral load 117 copies. The condition presented subacutely in almost 50% which included epilepsy, headache,

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**Table 3: CSF routine and special investigations on admission**

|  |  |
|--|--|
| CSF routine - microscopy -   |  |
| a. Pressure (mm H <sub>2</sub> O) : 100  |  |
| b. Proteins (mg / dL) : 91   |  |
| c. Glucose (mg / dL) : 50  |  |
| d. Leukocytes (cells per microlitre) : 30 (lymphocytes – 70%)  |  |
| CSF special investigations -   |  |
| a. ADA <sup>†</sup> : 8.5  |  |
| b. CRAG <sup>‡</sup> : Negative  |  |
| c. VDRL <sup>§</sup> : Negative  |  |
| d. Cytology for malignant cells : Negative   |  |
| e. HSV DNA PCR <sup>  </sup> : Negative  |  |
| f. JC virus DNA PCR : Negative   |  |
| Abbreviations: † Adenosine de-aminase, ‡ - Cryptococcal antigen, § - Venereal Disease Research Laboratory,    - Herpes simplex virus |  |

**Table 4: Special CSF investigations to diagnose CD8 encephalitis**

|   |  |
|---|--|
| Special CSF investigations : Values   |  |
| 1. CSF CD4 : 13.06 % (0.8 cell / mm <sup>3</sup> )                                      |  |
| 2. CSF CD8 : 75.45 % (4.9 cell / mm <sup>3</sup> )                                      |  |
| 3. CSF CD4 : CD8 ratio (Normal : 1.48 – 2.26) : 0.17                                    |  |
| 4. CSF HIV viral load (copies / ml) : 11,157  |  |
| (corresponding Plasma Viral load : 200 copies / ml and CD4 count : 525 for comparison ) |  |

coma, dizziness, confusion, dementia, mild memory disorders, neurologic deficit and “mood troubles”.<sup>4</sup> Our patient was a 55 year old with HIV for 10 years and a median CD4 of 460. He presented subacutely with memory disturbance and bipyramidal signs. The pyramidal signs were unique as it has not been reported in literature. These symptoms usually occurred during immune reconstitution (early in the course of therapy) or during treatment interruption<sup>4</sup> unexpectedly striking clinically and immunologically stable patients.<sup>3</sup> Our patient similarly presented when he was immunovirologically stable (Table 1) on second line ART for five years.

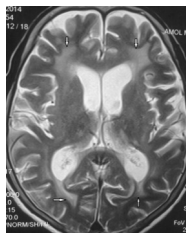
ART drugs have a CPE (CNS Penetration Effectiveness) score. As per studies, regimens with high CPE score are essential to achieve CSF HIV-1 RNA suppression.<sup>5</sup> Table 5 below<sup>6</sup> shows CPE scores of different ARV drugs. As per this table, the newer regimen had a CPE score of 8 [ABC/3TC/DRV(r)] compared to 6 of older regimen {TDF/FTC/ATV(r)}.

A close differential of CD8 encephalitis is ADEM (Acute Disseminated Encephalomyelitis). In CD8 encephalitis, T2-FLAIR hyperintensities are more diffuse and poorly delineated than large

**Table 5: CPE scores of different ARV drugs<sup>6</sup>**

| Drug class                                     | CPE score   |  |   |   |
|--|-------------|--|---|---|
|  | 4           | 3  | 2                                       | 1   |
| Nucleoside reverse transcriptase inhibitors    | Zidovudine  | Abacavir, Emtricitabine                              | Didanosine, Lamivudine, Stavudine       | Tenofovir, Zalcitabine  |
| Nonnucleoside 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  |   |   |

Letendre S Top Antivir Med. 2011 Nov;19(4):137-42.



**Fig. 1: T2 Weighted Axial image showing hyperintensities in bilateral periventricular white matter. Arrows show the periventricular hyperintensities more prominent over the frontal horns (front vertical arrows)**

and multiple lesions in ADEM, but the principal differences are the gadolinium-enhanced lesions. In CD8 encephalitis, they are thinner than 2 mm and could be missed if a post-contrast T1 spin echo-sequence with magnetization transfer is not performed. These faint enhancements follow perivascular spaces with a linear/punctate shape amidst the FLAIR hyperintensities whereas in ADEM, the enhancement is peripheral with a ring/incomplete ring-shaped form.<sup>3</sup> Our case had bilateral hyperintensities on T2-FLAIR and perivascular enhancement on post-contrast sequence which were diagnostic.

CSF pleocytosis in these patients comprised >90% lymphocytes which were mainly CD8 lymphocytes expressing the CCR5 phenotype. The mean CSF HIV viral load was 5,949 copies/ml in one study<sup>3</sup> and 2236 copies/ml in second<sup>4</sup> without any role of blood CD8 count.<sup>[3]</sup> Our case had a CSF HIV viral load of 11,157 copies/ml and disproportionately increased CSF CD8 cells.

In certain cases, the inflammation after HIV infection may overshoot its objective thereby becoming self-sustaining. Corticosteroids block this

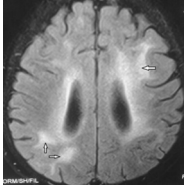
phenomenon. One study showed a mean survival time of 8 years<sup>3</sup> whereas other reported considerable improvement with steroids in one-third patients over a median follow up of four years.<sup>4</sup> Patients were treated with intravenous methylprednisolone followed by a tapering dose of prednisone (1 mg/kg for 2 months followed by a reduction of 5mg every 2 weeks) for a median period of 6 months as proposed in ADEM.<sup>3</sup> Our patient responded to methylprednisolone and is stable on follow up despite no long term oral steroids being administered.

### Conclusion

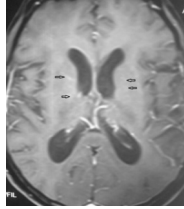
The triad of subacute diffuse severe encephalitis, CD8-cells in CSF and a diffuse leukoencephalopathy with restricted diffusion and perivascular contrast enhancement on imaging has been suggested as the diagnostic triad for CD8 encephalitis. Clinicians should recognize this as it is treatable by corticosteroids and ART modification.

### Abbreviations

3TC – Lamivudine; ADEM – Acute Disseminated Encephalo-Myelitis; ART – AntiRetroviral Therapy; ATV (r) - Atazanavir boosted with ritonavir; AZT – Zidovudine; CNS – Central Nervous System; CSF - Cerebrospinal fluid; CPE - CNS Penetration Effectiveness score; FLAIR - Fluid Attenuated Inversion Recovery Sequence; FTC – Emtricitabine; HAART - Highly Activated Anti-Retroviral Therapy; HAND - HIV Associated Neurocognitive Disorders; HIV - Human Immunodeficiency Virus; IRIS - Immune Reconstitution Inflammatory Syndrome; MMSE - Mini Mental Status Examination; MRI - Magnetic Resonance Imaging; NVP – Nevirapine; TDF - Tenofovir



**Fig. 2: T2 FLAIR Axial image. Arrow in the right hemisphere showing asymmetric hyperintensity in right periventricular and right fronto-parietal white matter. In the left hemisphere, hyperintensity in high parietal white matter indicated by the vertical arrow and hyperintensity in left parieto-occipital junction indicated by the horizontal arrow.**



**Fig. 3: Post gadolinium contrast T1 weighted image showing enhancement perpendicular to ventricular margins (arrows indicating enhancement better appreciated on the left side) most likely representing perivascular enhancement.**

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