HIV-associated neurocognitive disorder and HIV-associated myelopathy in a patient with a preserved CD4, but high viral load—a rarely reported phenomenon: a case report and literature review

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Abstract

Background: Despite widespread use of combination antiretroviral therapy (cART), HIV-associated neurocognitive disorder (HAND) and HIV-associated myelopathy (HAM) are not showing significant reduction in there occurrence. The HAM is a progressive myelopathy that often occur synchronously with severe form of the HAND in patients’ having advanced immunosuppression. However, co-existence of less severe form of the HAND and HAM in patient with relatively preserved CD4 cells is rarely reported clinical entity in post cART era.

Case presentation: We report a 16-year old male, acquired HIV infection vertically, was on second line regimen because of virological failure since 3 years. His current CD4 lymphocyte count is 835 cells/μL with viral RNA level of 33,008 copies/mL. Currently presented with progressive forgetfulness, gait imbalance, and a frequent staring episodes without loss of postural tone. Neurological examination was pertinent for cognitive dysfunction with score of 6 on International HIV Dementia Scale (motor speed = 3, psychomotor speed = 2, and memory recall = 1). Lower limbs power is 4−/5, increased deep tendon reflexes, and unsteady gait. Brain MRI revealed diffuse both cortical and white matter T2 and FLAIR hyperintense lesions. Thoracic MRI showed abnormal T2 signal prolongation spanning from mid thoracic cord to conus. Electroencephalography study showed severe generalized slowing with evidence of focal dysrhythmia in bilateral frontotemporal regions. Unremarkable serum vitamin B 12 level (286 ng/mL). Virological failure with the HAND, HAM and seizure was considered. Dolutegravir +3TC + ATV/r regimen and valproate for seizure disorder was started. On 6 months follow up evaluation, he is clinically stable with significant improvement of his symptoms related to seizure disorders and modest improvement of his cognitive dysfunction, as he is now attending his school regularly. However, less improvement was observed reading his gait abnormality.

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Background
HIV-Associated Neurocognitive Disorder is considered the most frequent cause of dementia for people less than 40 years old [1]. Neurocognitive disorders have a complex classification, however its demonstration by clinical, neuropsychological and neuroimaging methods is important, because the HAND is considered an AIDS defining illness, its presence affects compliance with treatment and it has also been observed that antiretroviral drugs could revert its progress [2]. HIV-associated myelopathy usually seen in patients with advanced HIV/AIDS and often presented with progressive symptoms suggestive of chronic myelopathy. These symptoms includes: spastic lower limbs, gait abnormality, and bladder dysfunction [3]. The thoracic segment of spinal cord is the most commonly involved part of the spinal cord. More specifically, the posterior and lateral columns of the spinal cord are vulnerable to white matter vacuolization neuropathological hallmark of the HAM. Moreover, its unique predilection for posterior and lateral columns of the spinal cord makes its diagnosis more difficult to differentiate from vitamin B12 deficiency which also has a close clinical and pathological resemblance to the HAM [4].

In the pre-cART era, the HAM usually developed in the advanced stages of the HIV infection with a progressive course until the patient’s death. Even though pathologic abnormalities of the HAM were found at autopsy in 22–55% of patients with advanced HIV infection [5, 6]. Up-to-date, there is no effective standard treatment of HIV-associated myelopathy, except symptomatic treatment of spasticity and bowel/bladder dysfunction. Nevertheless, few case reports suggested possible symptoms improvement of the HAM after initiation of cART [7, 8]. Even though, the severity and frequency of the HAND has decreased significantly in post cART era in developed world; the HAND is still a major cause of morbidity and mortality among HIV+ patients living in Low and middle income countries [9]. According to one study from South Africa, 45% of HIV+ youths met criteria for HIV-associated neurocognitive disorders [9].

Furthermore, simultaneous co-existence of the HAND and HAM in a single patient may have an additive effect in worsening patient quality of life and ultimately result in poor adherence to cART, which ultimately result in treatment failure. To our knowledge, this is the first case to be reported from Ethiopia. To this end, the aim of this case report is to shed a little light on the existing understanding of continuous occurrences of the HAND and HAM despite early initiation of cART and good immunological status, yet patient may have virological failure and may develop this AIDS defining major CNS complication.

Case presentation
We report a 16-year old male, HIV+ patient (vertical transmission) on second line combined antiretroviral therapy (cART), ABC/3TC + ATV/r regimen, with recent CD4 count of 835 cells/ul. He never had baseline viral load as the service was not available at his follow up area. He presented with progressive forgetfulness and gait imbalance over a period of 4 months. In addition, he has episodic loss of consciousness associated with sudden staring and automatism and hand tremor. He has blurring of visions and paresthesia of lower limbs. Past medical history was relevant for repeated admission for bacterial meningitis at a local hospital; after he presented with fever, headache, and neck pain. At a time he was investigated with CSF analysis, which was repeatedly suggestive of pyogenic meningitis. He was discharged after completion of full course of anti-meningeal dose of antibiotics. He denied any history of treatment for cryptococcal meningitis, no history of bowel or bladder dysfunction or history of upper limb weakness.

Neurological examination was pertinent for cognitive dysfunction with score of 6 on International HIV Dementia Scale (motor speed = 3, psychomotor speed = 2, and memory recall = 1). Patient’s functional status was not assessed formally by using standard tool. However, we have assessed his functional status by asking him about his daily activities, including home and school activities, he reported to have mild functional impairment, but able to live independent of anyone’s help for hid daily life. He fulfilled criteria for HIV-associated mild neurocognitive disorder (MND). Fully conscious and oriented with normal cranial nerves, lower limbs motor power was 4+/5, equivocal plantar responses, mildly increased tone, increased knee reflexes. Has an unsteady gait with flexed trunk and impaired tandem walk. He
used to be on cotrimoxazole prophylaxis (CPT) but dis-
continued shortly because he couldn’t tolerate the drug.

Routine hematological and serological tests were unre-
mrkable. Viral load is 33,008 copies/mL (Table 1). Brain
MRI revealed diffuses both cortical and white matter T2
and FLAIR hyperintense lesions, also minimally involving
cerebellum, without mass effect (Fig. 1a, b, c). Thoracic
MRI revealed abnormal T2 signal prolongation involving
the cord, spanning from mid thoracic to conus, which is
non-enhancing to contrast agent. Electroencephalography
(EEG) study showed severe generalized slowing with
evidence of severe focal dysrhythmia around bilateral
frontotemporal regions (Fig. 2), indicating generalized en-
cephalopathy related to the HAND.

The patient was treated for pulmonary tuberculosis 5
years back (diagnosed based on chest X-ray) and com-
pleted his drug regimen and declared cured. On current
spine MRI, there are no evidences of Pott disease, which
is often radiologically characterized by presences of:
wedged shaped vertebral fracture forming gibbus, para-
spinous enhancing mass compressing spinal cord mainly
in the lower lumbar region. Accordingly, our patient
does not have any of these radiological features to make
us suspect spine TB. Considering clinical presentations,
examination findings, brain and spine MRI findings,
EEG findings and higher viral load detection despite
fairly maintained CD4 count; the patient was diagnosed
as a case of virological failure + HIV-associated neuro-
cognitive disorder + HIV-associated myelopathy + seiz-
ure disorder. The patient was started on integrase based
regimen (Dolutegravir +3TC + ATV/r). In addition, val-
proate was started for seizure disorder and physical ther-
apy for spasticity. On 1 month follow up, the patient has
improvement in symptoms related to seizure disorders.
However, no significant clinical improvement was ob-
erved regarding cognitive and gait abnormality. The lat-
ter symptoms may take longer time to result in
observable clinical improvement.

Table 1 Patient’s Laboratory test, results and references

| Laboratory tests | Results | Reference range |
|-----------------|---------|-----------------|
| WBC             | 10,100 cells/mm³ | 4500–10,000 cells/mm³ |
| Platelet count  | 367,000 cells/mm³ | 150,000 to 450,000 cells/mm³ |
| Hemoglobin      | 14.1 g/dL | 14.0 to 17.5 g/dL |
| MCV             | 91.5 fl | 79.4–94.8 fl |
| Urea            | 9 mg/dL | 4.3–22.4 |
| Creatinine      | 0.5 mg/dL | 5.1–14 |
| SGOT            | 46 U/L | 0–35 U/L |
| SGPT            | 68 U/L | 0–35 U/L |
| Total bilirubin | 0.5 mg/dL | 0.3–1.0 mg/dL |
| Direct bilirubin| 0.09 mg/dL | 0.1–0.3 mg/dL |
| GGT             | 43 U/L | 9–50 U/L |
| VDRL            | Negative |
| HBSAg and anti HCV | Negative |
| CD4 cells       | 835 cells/μL | 500–1400 cells/μL |
| Viral load      | 33,008 copies/mL | < 50 copies/mL |
| Vitamin B 12    | 286 ng/mL | 200–900 ng/mL |

Discussion and conclusion
In the pre cART era, HIV-associated dementia occurred
in up to 20% of individuals with acquired immunodefi-
ciency syndrome (AIDS) and was almost always fatal
[10]. Today, HIV-associated dementia is rare in the de-
veloped world, occurring in fewer than 5% of patients
with HIV. This decrease is largely attributed to the wide
spread cART use, as patients with HIV who are on ART
perform better on neuropsychological testing than their
ART-naïve counterparts [11]. Early identification of
HAND is very crucial as un-treated HAND is associated
with morbidity and mortality. Moreover, presences of
the HAND may result in poor adherence to cART and
ultimately paving ways to development of drug resist-
ance [7]. In < 1% of patients, mainly in those with ad-
vanced HIV disease vacuolar myelopathy results in a
spastic paraparesis with immobility and incontinence [9].
Few case reports indicated, early identification and initi-
ation of cART may result in clinical improvement in pa-
tients suffering from the HAM [7, 8].

Our patient acquired HIV infection via vertical
transmission from his parents who themselves are
taking cART. His symptoms were progressive over 4
months, including insidious forgetfulness, lack of
motive and gait abnormality, which are consistent
with symptoms of HIV-associated neurocognitive dis-
order. Clinical features of HIV associated myelopathy
were masked by features of the HAM, but increased
lower limb tone, weakness and increased knee reflexes
in addition to thoracic MRI indicating T2 hyperinten-
sity supported our diagnosis of the HAM. Addition-
ally, the HAM is said to be highly mimicked by
vitamin B12 deficiency [4], but our patient had nor-
mal serum level of vitamin B12. To the author’s
knowledge, this is the first case to be reported from
Ethiopia. This case is unique not only because of the
co-occurrence of the HAND and HAM, but it also
supports the recent shift in clinical presentations of
HAND, especially in post cART era. The HAND
presenting with clinical features, traditionally thought to
be related to cortical dementias, like Alzheimer disease
[12]. Our patient predominantly presented with for-
gergetfulness and seizure disorders, both indicating cor-
tical involvement. So, we believe that this case report
would add to the understanding of the HAND and
HAM in our setup and open the door for future researches in an effort to understand these conditions.

In country such as Ethiopia, where issues of drug adherence and availability of less toxic and effective antiretroviral drugs are still a big challenge; it’s vital for practicing physicians to have high index of suspicion towards diagnosing the HAND and HAM. This should be true including for those HIV+ patients whom presented with clinical features suggestive of HAND, but have preserved cellular immunity (high CD4 cells count). This is especially relevant for children chronically infected with HIV as they have relatively normal CD4 counts. In addition, the clinical features of the HAND often mask prominent clinical features of the HAM. Therefore, it’s important to screen patients with HAND for possible coexistence of HAM. These practices will have a crucial public health importance, as early detection and optimal treatment of the HAND and HAM may result in clinical improvement, which will ultimately result in reduction in mortality and morbidity.

Literature review on the HAND and HAM from African studies
Despite better access to cART compared to decades back, prevalence of HIV-associated neurocognitive disorder in Africa is still unchanged, and resulting in more poor adherences to cART. According to a meta-analysis of studies on prevalence of the HAND in HIV positive patients on ART for more than 6 months in seven countries in sub-Saharan Africa (Uganda, Zambia, Malawi, Botswana, Nigeria, Cameroon and South Africa), prevalence of neurocognitive impairment was more than 30% [13]. In Ethiopia, between years 2016 to 2019, total of 4
studies were published on prevalence of HIV-associated neurocognitive disorder among HIV + adults on cART at four different ART clinics located in the country by using International HIV Dementia Scale (IHDS) as screening tool. According to these studies, the prevalence of HIV-associated neurocognitive disorder was, 33.3% [14], 35.7% [15], 36.4% [16], and 67.1% [17].

According to one systematic review done on 19 studies conducted in Africa, HIV myelopathy was described in 3–16.9% of patients whom presented with myelopathy in Ethiopia and South Africa. Their diagnosis was based on clinical and neuroimaging evidences of HAM in patients with advanced immune suppression (CD4 < 200 cells/ml) and after other potential mimickers are ruled out [18, 19]. Those countries without advanced neuroimaging facilities, diagnosis of HIV myelopathy was made in those patients who are HIV positive and presented with clinical signs and symptoms of myelopathy and no other causes of myelopathy were identified. In these studies, the proportion of myelopathy patients with HIV infection ranged from 14.1% in Nigeria [20], 30% in Ethiopia [18], to 50% in South Africa [21], these indirectly indicate the burden of HIV infection in these countries. Zenebe et al. [22], reviewed 130 patients admitted for spinal cord lesion between 1990 to 1993 to Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, to determine causes of spinal cord lesion. The authors reported, tuberculous spondylitis as the leading cause accounting for 35 (26.9%), and HIV associated myelopathies as the second common underlying etiology accounting for 22 (16.9%) of spinal cord disease.

Abbreviations
MRI: Magnetic resonance imaging; cART: Combined antiretroviral therapy; HAND: HIV-associated neurocognitive disorder; HAM: HIV-associated myelopathy; HIV: Human immunodeficiency virus; AIDS: Acquired immunodeficiency syndrome; CD4: Cluster of differentiation; HAD: HIV-associated dementia; IHDS: International HIV Dementia Scale; EEG: Electroencephalogram; ART: Antiretroviral Therapy; STC: Lamivudine; ABC: Abacavir; ATV/r: Atazanavir with Ritonavir booster; DTV: Dolutegravir; RNA: Ribonucleic Acid

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Authors’ contributions
BA, WA and LG, participated in evaluation, investigation, management, and follow up of the patient, and manuscript editing and preparation and all authors have read and approved the manuscript before submission.

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