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Case Report

Cerebellar Ataxia in HIV Patient due to Suspected Efavirenz Associated Neurotoxicity

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ABSTRACT

Objective: To report a rare presentation of efavirenz associated cerebellar ataxia in a patient of HIV/AIDS.

Background: A 35-year-old gentleman presented with one week history of acute onset cerebellar atxaia. Neurological examination revealed scanning speech, dysmetria, dysdiadochokinesia, gait ataxia and irrelevant talking. No sensory or motor deficit was present. Patient was a known case of Pulmonary kochs and HIV AIDS, already on antiretroviral and anti-tubercular treatment. Patient was taking Efavirenz 600 mg daily along with Tenofovir and Lamivudine for HIV. No abnormality was found on MRI brain with contrast. Chest X-ray and abdominal ultrasonography was normal. CD4 count was 520 cells/microlitre. CSF examination revealed mildly elevated protein (62 mg/dl), normal sugar (68 mg/dl) and normal cell count. CSF for AFB, bacterial culture, GenXpert, fungal culture, India ink was negative.

Discussion and Conclusion: For a known case of HIV AIDS on antiretroviral treatment, in the absence of any structural abnormality on MRI brain, a possibility of cerebellar dysfunction as a result of efavirenz associated neurotoxic side effect can be considered.

Keywords: Cerebellar ataxia; Neurological examination; Dysmetria; Dysdiadochokinesia

INTRODUCTION

Acute cerebellar ataxia (ACA) is a disorder that occurs when the cerebellum becomes inflamed or damaged. The cerebellum is the area of the brain responsible for controlling gait and muscle coordination. The term ataxia refers to a lack of fine control of voluntary movements. Here we present a case report of a rare presentation of efavirenz associated cerebellar ataxia in a patient of HIV/AIDS.

CASE REPORT

In May 2018, a 35-years-old gentleman presented to us with history of ataxic gait, ataxic dysarthria, tremulousness of hands on reaching out to objects and irrelevant talking for last one week. The illness was acute in onset and progressive in course. Patient was a known case of pulmonary kochs started on Isoniazid, Rifalmpicin, Pyrazinamide, Ethambutol 2 months back. Patient was also a known case of HIV AIDS taking Tenofovir, Efavirenz and Lamivudine for last one month.

There was no history of fever, headache, visual disturbances, seizures, and weakness of any limbs, sensory complaints, and bladder bowel involvement. Patient was nonalcoholic, non-smoker and had no history of drug abuse. His family history was unremarkable.

Examination findings

Pallor, cyanosis, clubbing, lymphadenopathy, pedal edema were absent. GCS was 15/15. Patient was conscious, but irritable. Memory was normal. Cognition was preserved. Sleep cycle was found to be disturbed. There were no meningial signs. His cranial nerves were intact. Fundus examination was normal. Speech was slow and scanning type. His gate was broad based and ataxic. Dysmetria and dysdiadochokinesia was evident. Tandem walking was impaired. Finger nose finger test and heel shin test was positive.

Nystagmus was present. There was no sensory or motor deficit. Plantars were bilateral flexor. Deep tendon reflexes were normal.

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Investigations

Serum bilirubin was normal but liver enzymes were mildly raised (less than two times of the upper limit of normal range). Renal function, lipid profile, blood glucose, thyroid profile, Serum vitamin B_{12} levels were all in normal range. Venereal Disease Research Laboratory test was non-reactive. HBsAg and Anti HCV were negative. ANA was negative.

Patient was a known case of HIV already on ART for last one month. His CD_4 count at the time of presentation to our hospital was 520 cells/microlitre. Brain MRI with contrast was normal. There was no evidence of cerebellar degeneration, focal lesion, demyelinating changes or hyper intensities on MRI. Chest X-ray and abdominal ultrasound was normal.

Examination of CSF revealed protein concentration of 62.5 mg/dl, glucose concentration of 68 mg/dl, and WBC count of 5 cells/mm^3. Bacterial culture of CSF samples showed no growth, and the results of Gram staining of CSF were negative. PCR analysis of CSF for herpes viruses (HSV 1 and HSV 2) were negative. CSF India ink and cryptococcal antigen was negative. CSF AFB and GenXpert was negative.

DISCUSSION

Ataxia in a patient of HIV is generally secondary to an infectious, vascular or neoplastic cause. Most infections are opportunistic and unlikely to occur when CD_4 levels are adequate. Focal lesions resulting from opportunistic infections such as toxoplasmosis and progressive multifocal leukoencephalopathy or primary CNS lymphoma were excluded as MRI brain was normal. Other metabolic causes were excluded with relevant investigations. Absence of fever and prodormal symptoms makes diagnosis of cerebellitis or brainstem encephalitis unlikely [1].

To rule out possible paraneoplastic etiology, patient was evaluated for any primary. On examination there was no palpable lymph node, testicular mass or thyroid nodule. Chest X-ray and ultrasound abdomen were also normal. Stool of occult blood was negative and PSA was within normal limits.

There have been reported cases of Opsoclonus myoclonus ataxia syndrome associated with mycobacterium tuberculosis in a patient of HIV. However, MRI Brain in such cases was abnormal, demonstrating hyper intensities within cerebellar hemisphere.

Cerebellar involvement can also be seen with HIV-associated neurocognitive disorder and directly HIV associated cerebellar dysfunction. We had reported a similar case of cerebellar ataxia [2] in a middle age male with CD_4 count 171 and no structural abnormality found in MRI. It was proposed that the cerebellar ataxia could be directly HIV related, which is still a possibility here.

However, in this particular case, patient is taking efavirenz along with isoniazid. His CD_4 counts are adequate. No structural lesion is seen on MRI. Hence, a possibility of neuropsychiatric side effect of efavirenz exacerbated by isoniazid cannot be undermined.

As per standard guidelines, HIV-infected adults in India are prescribed 600 mg efavirenz at a fixed-dose combination (FDC) with tenofovir and lamivudine.

Efavirenz is known to cause neuropsychiatric side effects including hallucinations, suicidal ideation [3], encephalopathy and ataxia [4]. Most neurotoxic side effects of efavirenz are reported to occur within the first 2-4 weeks after starting efavirenz [5].

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI). It has a long half-life and is prescribed as a once-daily dose of 600 mg. It is metabolised in the liver via the cytochrome p450 system, predominantly via CYP2B6. Loss of function single nucleotide polymorphisms in CYP2B6 leads to high efavirenz concentrations, which increases risks of toxicity [6]. Efavirenz toxicity occur more commonly in populations with a high prevalence of CYP2B6 slow metabolizer genotypes, like India [7]. It has also been seen that patient with CYP2B6 slow-metabolizer genotypes, who are taking isoniazid along with efavirenz have higher efavirenz concentrations [8].

In the given clinical scenario, in the absence of any obvious structural lesion or opportunistic infection and given the fact that patient is already on efavirenz and isoniazid and the combination is known to cause neuropsychiatric side effects, including ataxia, we propose efavirenz associated neurotoxicity as the possible etiology for cerebellar dysfunction.

Genetic analysis for CYP2B6 and Serum efavirenz levels were required for the confirmation of our diagnosis, the facilities of which were not available in our hospital setup.

Despite the above limitation, this case is significant because there have been very few case reports on efavirenz associated cerebellar dysfunction all over the world and no case report per se from India as per our knowledge. Besides, this case also sheds a light on possible role of isoniazid in accentuating neuropsychiatric side effects of efavirenz [9].

CONCLUSION

Any HIV patient presenting with ataxia should be thoroughly investigated. MRI brain should be done to exclude any degeneration, demyelinating changes or focal lesion. CSF studies should be done to rule out any opportunistic infection. For a known case of HIV on antiretroviral treatment, if above investigations fail to reach to any conclusion, a possibility of cerebellar dysfunction as a result of efavirenz associated neuropsychiatric side effect can be considered. It is recommended that patients weighing less than 40 kg should be prescribed a reduced dose of 400 mg. Efavirenz concentrations should be measured and if efavirenz concentration assays are unavailable, efavirenz dose should be reduced or totally withdrawn and patient be switched over to protease inhibitors.

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