Efavirenz-Induced Delayed Onset Cerebellar Ataxia and Encephalopathy

A 23-year-old woman with persistent latent HIV infection on Highly Active Anti-Retroviral Treatment (HAART) since 2009 was admitted with a 3-week history of progressive and severe imbalance on walking. Gradually, she developed total inability to walk or stand without support. She developed dysarthria for one week and had excessive somnolence. There was no history of fever, headache, vomiting or seizures. She reported a gradual loss of weight of nearly 5 kilograms (kgs) in the last 2 years. There was no history of alcohol, substance abuse or any other recent drug exposure. On examination patient was thin built with a weight of 28 kgs and a body mass index (BMI) of 13.8. She was easily arousable and well oriented, however a detailed cognitive assessment could not be performed due to poor attention. She was afebrile and there were no meningeal signs. She had hypermetric saccades and broken pursuits with scanning type dysarthria. Power as assessed by Medical Research Council (MRC) grading was normal in all 4 limbs; however, there was lower limb hyporeflexia. Patient had postural and intentional tremors of the hands. She had severe truncal and limb ataxia and Romberg's sign could not be assessed. Sensory examination revealed a mild proprioceptive loss in the feet, with normal touch and pain sensations. On application of the scale for assessment and rating of ataxia (SARA score) she had a score of 24 which indicates severe disability. A clinical diagnosis of cerebellar ataxia with encephalopathy was made and patient was evaluated. A non-contrast MRI brain and spine as well as CSF analysis was normal. Nerve conduction study showed a distal motor and sensory axonal neuropathy. Patient's haematological and metabolic parameters including sugar, thyroid and anti TPO levels, liver and renal function tests, and B12 and ammonia levels were normal. Serum and CSF VDRL was negative. Patient had been on HAART since 2009, and the regimen since 2017 consisted of tenofovir 300 mg lamivudine 150 mg and efavirenz 600 mg. Her CD 4 count was 193 and HIV viral load was not detected. On reviewing the literature, we came across a few cases of delayed efavirenz neurotoxicity. On application of the Naranjo's algorithm a total score of 6 was obtained which indicated a probable adverse drug reaction to efavirenz.[1] Efavirenz induced encephalopathy and cerebellar ataxia with HIV related poylneuropathy was considered as a possible diagnosis. Efavirenz levels could not be tested at our centre as the test is not commercially available. Efavirenz was replaced with dolutegravir. Four weeks later patient had significant improvement in symptoms with a SARA score of 6. She was able to walk independently, dysarthria completely resolved and there was mild finger nose in coordination and minimal impairment in tandem gait. A re-challenge with efavirenz was considered unethical, though it is a requirement for Naranjo's algorithm to prove causality of a drug-related adverse event.[1]

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) which inhibits HIV replication.[2] It is known to cause acute and transient neuropsychiatric side

effects which resolve over 8–12 weeks of starting treatment and do not necessitate a discontinuation of the drug.[3] The mechanism of neurotoxicity is not well elucidated; however, research has shown that mitochondrial toxicity due to oxidative stress may contribute to its adverse effects.[4] Late onset efavirenz induced neurotoxicty has been recently identified in HIV patients. Variava *et al*. have described a case series of 20 HIV patients who presented with subacute ataxia and encephalopathy due to efavirenz.[5] All of them were women with a median weight of 34 kgs and had received efavirenz for a median of 2 years (1–5.5). They had high plasma levels of efavirenz and ataxia resolved at a median of 2 months (IQR 1.25–4) after stopping the drug. In another case report from South Africa efavirenz induced ataxia was identified in two girls, 6 and 13 year old who had received the offending drug for 1 and 1.5 years, respectively.[6] Hammond CK *et al*. in an analysis of 12 HIV children with neurocognitive manifestations while on efavirenz treatment have identified delayed toxicity in two patients [Table 1].[7] Our patient too was a malnourished young woman who had received efavirenz for the last 3 years. Measuring efavirenz serum levels was not feasible at our centre. Since there was almost complete resolution of symptoms after changing the ART regimen, we can infer that she probably had chronic efavirenz toxicity.

Plasma concentration of NNRTI drugs such as efavirenz and nevirapine are influenced by genetic polymorphism, gender and weight of the patient. Efavirenz is metabolised by cytochrome P450 isoenzyme 2b6 to 8-hydroxy-efavirenz which along with the parent drug is responsible for the neurological side effects. Patients with G to T change at codon 516 of CYP2b6 gene have been found to have high efavirenz serum levels which correlate to initial neurotoxicity.[8] Slow metabolizers due to the presence of G/T or T/T allele are more frequently found in Africans, Indians

Table 1: Cases of delayed efavirenz toxicity reported in literature

Author, Year	Age, sex, ethnicity	Weight Kgs	Duration of Efavrienz treatment (months)	HIV Viral load (VL)/ CD4 count	Investigations	Clinical features	Efavirenz levels* mg/L (1-4 normal range)	Outcome
Variava, E. *et al*. 2017[5] case series : 20 patients	Age 30.5 years (24-36) all women South African descent	37.9 (34-42.6)	24 (12-66)	17 patients suppressed HIV levels	CSF: Normal in all. Brain imaging (19) : 9 normal 7:generalized atrophy, 1: cerebellar atrophy, 1: pineal cyst, 1:encephalitis (normal CSF)	Ataxia: all patients Encephalopathy: 11 patients	15 pts : >20 5 pts>4	Most improved One rechallenged with 400 mg 2 pts had recurrence on restarting efavirenz 3 died (1 due to other cause, 2 death cause not defined)
Hammond CK. *et al*.[7] 2019	1. 3-4 years African male 2. 8-9 years Africa female		20 months 28 months	CD4 : 1549/ uL VL<5copies/ mL CD4: 37%	CT brain: Normal MRI: non specific T2 Hyperintensity right peritrigonal white matter	Ataxia slurred speech Drowsiness Poor memory concentration	69 >20	Efavirenz discontinued Ataxia resolved Drowsiness resolved Neurocognitive deficits did not improve
Hauptfleisch MP. *et al*.[6] 2015	6 year old African female 13 year old African female		12 months 18 months	CD4 :250/uL VL: <100copies/ mL CD4: 554 VL: 28 copies/mL	MRI CSF: normal MRI CSF: Normal	subacute ataxia Ataxia	69.1 16.2	Efavirenz discontinued Ataxia resolved
Cross HM *et al*.[12] 2018 Case series: 7 women with concomittant INH therapy	Age Median 43 IQR (36-47) African Women	Weight 59 (55-62)	34 (17-48) INH prophylaxis 6 (2-9)	All pts virally suppressed	MRI normal/ nonecific CSF: normal	Ataxia Drowsiness Psychomotor slowing	All pts supratherapeutic efavrienz levels	Efavirenz discontinued in all INH discontinued in 5 All symptoms resolved

*Genetic test for CYP2b6 mutation not done in any patients

and Hispanics populations. In a study from South India, T allele homozygosity was found to be more common in Indians compared to South East Asians or Americans.[9] Nemaura *et al*. have shown that in addition to T allele homozygosity, female gender and weight less than 62 kg is associated with high efavirenz serum levels and have proposed an algorithm for dose reduction in these patients.[10] There are several studies which have aimed at reducing efavirenz dose based on genotying and therapeutic drug monitoring.[11] However, since most patients develop tolerance to the initial neuropsychiatric side effects despite the high plasma levels of the drug, the clinical implications of genotying or dose adjustments were not very clear. A recent study has identified seven South African women with subacute encephalopathy and cerebellar ataxia while on treatment with efavirenz who were recently started on isoniazid.[12] All patients had supratherapeutic efavirenz levels. Isoniazid (INH) inhibits metabolism of efavirenz through inhibition of CYP2A6, which probably is an important alternate pathway for slow metabolisers with mutations in CYP2B6 gene. All patients improved on withdrawal of the drugs and in two patients isoniazid was reintroduced without any recurrence of symptoms. With the increasing awareness of a delayed neurotoxicity which correlates with plasma efavirenz levels and requires the withdrawal of the drug, genetic studies to identify T allele homozygosity may be important. Therapeutic drug monitoring is not a routine practice in India. Our case suggests that in young genetically susceptible patients who are underweight, especially in women, a therapeutic drug level monitoring to adjust the dose of efavirenz may be required to prevent delayed drug toxicity.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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