Late-onset efavirenz neurotoxicity

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SUMMARY

Efavirenz is a commonly used antiretroviral drug in Malaysia. It is used to treat Human Immunodeficiency Virus infection alongside with two nucleoside reverse transcriptase inhibitors (NRTI). Efavirenz is well recognized to cause transient neuropsychiatric side effects early during the initiation. Recently, cases of delayed-onset neurotoxicity with similar clinical syndromes caused by efavirenz have been reported, primarily in the South African population. Here we present a case of a Malaysian lady living with HIV treated with an efavirenz-based ART who presented with late onset encephalopathy and ataxia, which improved significantly after the withdrawal of efavirenz.

INTRODUCTION

The number of people living with HIV in Malaysia was estimated to be at 81,942 in year 2022 and it has been reported that 66% of them were receiving antiretroviral therapy (ART).[1] Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that can inhibit HIV replication. It is widely used as part of the first line ART to treat HIV in Malaysia.[2] Acute and transient neuropsychiatric side effects were often reported after initiating efavirenz based treatment.[3] The common side effects include giddiness, attention deficit, headache, sleep disturbance, and depressed mood, but they are usually mild and resolve after few weeks of exposure.[3] However, lately there have been reports of patients who developed ataxia and encephalopathy which were attributed to efavirenz induced neurotoxicity. Ebrahim Variava et al. and Lyneshree Munsami et al. described cases of late onset efavirenz toxicity in South Africa which involves 20 patients and 40 patients respectively.[4-5] A case report from India also documented delayed-onset cerebellar ataxia and encephalopathy after 3 years of efavirenz therapy.[6] Despite efavirenz being widely used in Malaysia, there has been no similar report of ataxia or encephalopathy until now.[7] Here we report likely the first case of late onset efavirenz neurotoxicity in Malaysia.

CASE PRESENTATION

We encountered a 56-year-old lady with underlying type 2 diabetes mellitus on insulin and HIV positive on antiretroviral therapy (ART). She was first diagnosed with HIV in 2020 via contact tracing and was then started on an ART regimen of oral tenofovir 300mg, emtricitabine 200mg, and efavirenz 600mg daily. After 2 years of treatment, she presented with 2-month history of slurred speech and progressive body weakness requiring wheelchair for ambulation. She had poor appetite and weight loss (49 to 44kg). There was otherwise no history of fever, vomiting, cough, or visual disturbance. She was not on any other medication or supplement. On examination, she was emaciated, orientated with a full Glasgow Coma Scale (GCS) but was slow in responding and had a scanning speech. Neurological examination demonstrated reduced power symmetrically at all four limbs with a Medical Research Council (MRC) grading of 4/5. She had generalized hypotonia and hyporeflexia. Her coordination was also abnormal with truncal ataxia and dysdiadochokinesia. Otherwise, her sensations and cranial nerves examinations were normal. She had a Mini Mental State Examination (MMSE) score of 14/30 indicating moderate cognitive impairment.

Her full blood count, renal profile, and liver function test were unremarkable. Her repeated CD4 count was 549, and her HIV viral load remained suppressed. She had a normal C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), thyroxine (T4), thyroid stimulating hormone (TSH) and creatine kinase (CK) levels. Rapid plasma reagin and treponemal test were negative. She had a Hemoglobin A1c (HbA1c) of 7.2%. Her chest X-ray was also normal. Her MRI Brain showed old lacunar infarct within both frontal lobes, which was not consistent with her neurological findings. A provisional diagnosis of efavirenz induced encephalopathy was made. However, efavirenz level was not available in our centre. Other differential diagnosis included HIV associated neurocognitive disorder (HAND), HIV myelopathy, and paraneoplastic syndromes. Nonetheless, her efavirenz was withdrawn and switched to dolutegravir. She was offered for a lumbar puncture to further investigate but she declined.

She was seen back in the clinic 2 weeks later, showing overall improvement clinically with improved strength, speech, memory, and appetite. Her MRI cervical revealed cervical spondylosis with mild central canal stenosis at C5/C6 level but there was no cord compression. Her electroencephalogram (EEG) revealed mild generalized cerebral dysfunction, with bifrontal focal slowing which was suggestive of encephalopathic changes. Her vitamin B12 level was normal and folate level was low (3.5nmol/L). However, her symptoms had already improved prior to folate supplementation. Other workup including a paraneoplastic autoimmune profile was negative. As for her positive anti-nuclear antibody (ANA), she did not exhibit any clinical feature of connective tissue disease. Furthermore, her anti-dsDNA antibodies and extractable nuclear antigen (ENA) were negative. By applying the Naranjo Adverse Drug

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Table I: Naranjo Adverse Drug Reaction Probability Scale

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
	Total Score : 5			
Interpretation: Definite ≥ 9 Probable 5-8 Possible 1-4 Doubtful ≤ 0				

Reaction Probability Scale, a score of 5 was obtained (Table 1), indicating a probable adverse drug reaction from efavirenz.8 At 3 months after withdrawal of efavirenz, her symptoms had totally resolved and she was able to resume her activities of daily living independently. Her neurological examination also demonstrated resolved encephalopathy, cerebellar sign and limb weakness.

DISCUSSION

We described a case of a Malaysian lady with HIV who was treated with an efavirenz based ART and presented 2 years later with encephalopathy and ataxia, which improved significantly after the withdrawal of efavirenz. These findings are consistent with the cases reported from other authors recently (Table II). In the case series from South Africa, which consist of 20 and 40 patients respectively, most of their patients presented with ataxia and encephalopathy after being on efavirenz treatment.[4-5] The degree of encephalopathy can vary from mild confusion and psychomotor retardation to coma. Some patients even had mood disturbances or psychotic symptoms prior to the onset of ataxia and encephalopathy.[9] Similar to the previous reports, our case also presented as late onset and had a subacute presentation.[4-5,9] The duration of efavirenz treatment prior to the presentation of encephalopathy or ataxia can vary from 5 months to more than 5 years.[4-5,9] All those patients had supratherapeutic plasma efavirenz level.[4-5,9] Unfortunately, we were unable to measure efavirenz level in our patient because the test is not available in our centre. Similar to our case, further investigations did not yield any other aetiology to explain the presentation, and most of the patients showed improvement after efavirenz was withdrawn. Despite that, mortality has been reported to be as high as 15% due to complications from efavirenz neurotoxicity in the South Africa cohort.[5-6]

Efavirenz has been known to cause CNS toxicity, resulting in neuropsychiatric symptoms. However, the exact mechanism of efavirenz causing neurotoxicity is still unclear and some studies suggested that the neurotoxicity is mediated by oxidative stress and mitochondrial dysfunction.[3] Based on the case series in Africa, several risk factors for late onset neurotoxicity have been suggested, including concomitant isoniazid use, low body weight, and female gender.[4-5] This association is also supported by a recent study which also found that slower metabolism of efavirenz due to mutations in CYP2B6 gene is strongly associated with late onset efavirenz neurotoxicity.[10] Efavirenz is primarily metabolised through the CYP2B6 enzymes, which contribute to more than 90% of efavirenz metabolism whereas less than 8% of efavirenz is metabolised by the CYP2A6 enzyme.[3] CYP2B6 slow metabolizer due to genetic polymorphism is associated with a higher plasma efavirenz level, and these slow metabolizer are more frequently found in the African, Hispanics and Indian populations.[3] Hence CYP2A6 enzyme became an important role to metabolise efavirenz in those with impaired CYP2B6. Isoniazid use can inhibit the CYP2A6 enzyme, which causes raised plasma efavirenz level in those with genetically slow metabolizer. Our patient did share some risk factors for late onset efavirenz neurotoxicity which is low body weight (49kg) and female gender. She did have concomitant isoniazid use for tuberculosis preventive therapy, but the last usage was one year prior to the symptom onset. We were also unable to establish if our patient has genetic mutation in the CYP2B6 gene nor ancestry link to Africa or India.

This case report highlights a significant yet underrecognized issue of late-onset efavirenz neurotoxicity, which has not been previously documented in Malaysia. As efavirenz remains a commonly used antiretroviral medication, this study underscores the importance of monitoring for delayed neurotoxic effects even after prolonged period of treatment. This report provides valuable insights that may prompt clinicians to consider efavirenz-induced neurotoxicity in their differential diagnosis for patients presenting with late-onset neurological symptoms. Furthermore, it emphasizes the need for further research into the risk factors and mechanisms behind efavirenz neurotoxicity, particularly in diverse populations.

Table II: Reported cases of Late-onset efavirenz neurotoxicity

Author, Country	Age, Sex	Weight (Kg)	Duration of efavirenz treatment	CD4 count/ HIV Viral Load (VL)	Clinical features	Efavirenz level (mg/L) *normal range 1-4	Investigations	Outcome
Variava, E. et al. 2017.[4] 20 patients. South Africa.	Age: 24-36, all female	34.1-42.6	12-66 months	Median CD4: 299, 17 patients had supressed VL	Ataxia: all patients Encephalopathy: 11 out of 20 patients	Supratherapeutic in all patients	Brain imaging : 9: normal 7:generalized atrophy, 1: cerebellar atrophy, 1: pineal cyst, 1:encephalitis CSF: 19 – normal, 1 - clotted	Improved once efavirenz withdrawn. 2 had recurrence when rechallenged. 3 died.
Lyneshree Munsami et al. 2023.[5] 40 patients. South Africa.	Mean age: 42.1 3 male, 37 female	Not available	17 patients: <12 months 17 patients: >12 months 6 patients: unknown	26 out of 40 CD4>200, 34 out of 40 VL suppressed	Ataxia: 33 patients Encephalopathy: 19 patients	Supratherapeutic in all patients (8-96)	33 Brain imaging: normal/ non-specific 34 lumbar puncture: 28: normal, 3 : non-specific abnormalities, 2: pleocytosis and elevated protein 1: treponema pallidum positive 8 out of 9 EEG: diffuse slowing	32: recovered on average 2 weeks after efavirenz was withdrawn. 1: remained severely ataxic 4: passed away
GRK Sarma et al. 2022.[6] India.	23, female	28	>24 months	CD4: 193 VL: not detected	Psychosis: 4 patients Ataxia with encephalopathy	Not available	Brain imaging: Normal CSF: normal	Improved 4 weeks after efavirenz was withdrawn
HM Cross et al. 2018.[9] 7 patients. South Africa.	Age: 36-47 All female	55-62	17-48 months	CD4: 324-462 All VL supressed	Ataxia with psychomotor slowing. 2 patients had mood and psychotic symptoms.	Supratherapeutic (>20)	Brain imaging: Normal/non-specific CSF: normal EEG: generalised (predominantly theta) slowing	Improved after a median of 14 days after efavirenz withdrawal
Our patient (Malaysia)	56, female	49	24 months	CD4: 549 VL: supressed	Ataxia Psychomotor retardation	Not available	MRI : non-specific CSF: not done EEG: mild generalised cerebral dysfunction	Improved 2 weeks after efavirenz was withdrawn

CONCLUSION

This case report presents the first documented instance of late-onset efavirenz neurotoxicity in Malaysia, adding to the growing body of evidence highlighting this condition. Our findings emphasize the necessity for clinicians to be vigilant for late-onset neurological symptoms in patients on long-term efavirenz therapy. Early recognition and prompt discontinuation of the drug can lead to significant clinical improvement, as demonstrated in this case.

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DECLARATION

The authors declare no conflicts of interest related to this publication.

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