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Late efavirenz-induced ataxia and encephalopathy: a case series

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Abstract

Background—WHO treatment guidelines recommend efavirenz in first line antiretroviral therapy (ART). Efavirenz commonly causes early transient neuro-psychiatric adverse events. We present 20 cases with severe encephalopathy accompanied by ataxia due to efavirenz toxicity

Methods—Consecutive HIV-infected adults taking efavirenz-containing ART admitted to Tshepong hospital, Klerksdorp, South Africa with ataxia and encephalopathy were included in this case series.

Results—We identified 20 women admitted to hospital with severe ataxia. All received efavirenz-based ART for a median of 2 years. All had severe ataxia and none had nystagmus. Eleven had features of encephalopathy. Median weight was 34kg (IQR:29.7–35.3); median CD4 count 299 cells/mm³ (IQR:258-300) and most (18 of 19) were virally suppressed. Eight patients had a record of prior weights and 7 of 8 showed significant weight loss with a median weight loss of 10.8 kg (IQR:8–11.6). All cases had plasma efavirenz assays, 19 were supra-therapeutic (more than twice upper level of therapeutic range) and 15 had concentrations above the upper limit of assay detection. Ataxia resolved after withdrawal of efavirenz at a median time of 2 months (IQR: 1.25–4), and recurred in two of three patients when rechallenged. Admissions prior to diagnosis were frequent with 10 cases admitted previously. Three women died.

Conclusion—Efavirenz toxicity may present with severe reversible ataxia often with encephalopathy years after its initiation; likely in genetic slow metabolizers. We recommend that patients whose weight is <40kg receive lower doses of efavirenz and that therapeutic drug monitoring (TDM) be considered, and efavirenz stopped in patients presenting with ataxia.

Roles of authors: EV proposed the case series, identified most patients and wrote the manuscript. FS and PM contributed to the identification of patients and collection of patient data and reviewed the manuscript. MR collected data and shipped specimens. JN received and processed specimens. GM, NM, and AM assisted in the analysis, provided research support and co-wrote the manuscript.

BACKGROUND

Guidelines for the treatment of HIV-infected adults in low to middle income countries recommend the non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz (efavirenz) as backbone therapy, combined with tenofovir disoproxil fumarate and either lamivudine or emtricitabine¹. In most settings, three antiretrovirals are administered as a single tablet in a fixed dose combination (FDC), reducing pill burden, costs and improving adherence² but also ensuring that dose adjustments are limited.

Efavirenz commonly causes transient neuro-psychiatric side effects, usually shortly after treatment initiation, which are usually mild to moderate in severity^{3,4}. More recently it has been recognized that efavirenz, especially its 8-OH metabolite, can cause neuronal toxicity.⁵ We describe a case series of 20 patients with severe ataxia with encephalopathy and from a single centre over a 20 month period, all whom had high efavirenz concentrations. This case series suggests that severe ataxia and encephalopathy due to toxic efavirenz concentrations has been under-recognised and presents with a clear clinical phenotype.

METHODS

We conducted a chart review of patients with suspected efavirenz-induced ataxia and encephalopathy admitted to the 220 bed Department of Internal Medicine at a secondary level hospital (Tshepong) in Klerksdorp, South Africa where over 24,000 individuals are receiving antiretroviral therapy in the public sector (Annual Performance Plan subdistrict Malosana North West Province South Africa Dec 2016). The case definition used was: onset of ataxia while on efavirenz-based ART; no other cause of ataxia identified; and reversal of symptoms with withdrawal of efavirenz. Other causes of ataxia were excluded (hypothyroidism, vitamin B12 deficiency, alcohol abuse, neurosyphilis, intracranial mass lesions, and malignancy with paraneoplastic manifestations). Ataxia was defined as being truncal if unable to balance when sitting, standing or walking, or limb ataxia as having intention tremor, dysmetria and dysidiadokinesia. All patients had efavirenz discontinued and had plasma efavirenz concentrations taken within one to three days after their last efavirenz dose. Efavirenz concentrations were measured on these specimens batched a few weeks after the blood draw, using liquid chromatography with tandem mass spectrometry as previously described in the University of Cape Town Division of Clinical Pharmacology's accredited laboratory in South Africa⁶. The upper limit of the assay was 20 mg/L and therapeutic efavirenz concentrations were defined as 1–4 mg/L⁷

RESULTS

Between January 2015 and August 2016, we identified 20 adult women admitted to hospital with severe ataxia who were receiving efavirenz-based ART. Eleven women had truncal ataxia of which eight were unable to sit unaided, five had limb ataxia and 4 had both truncal and limb ataxia. Eleven women had features of encephalopathy with impaired consciousness, psychosis and delirium during some part of their stay. Their median age and weight was 30.5 years (24.0–36) and 37.9 kg (34.1–42.6) respectively. In 8/20 women, a prior weight was able to be abstracted from clinical records 6–12 months prior to admission;

seven had weight loss, and their median weight loss was 10.8 kg (IQR: 8–11). Their median duration of efavirenz treatment was 2.00 years (1.00–5.5), and 17 of 20 women were virally suppressed although two of the did not have a recent viral load result.

We were unable to find an alternative cause for cerebellar signs in virtually all women. The CSF of nineteen women had no abnormal findings, and one was clotted. Brain imaging was available from the admission of 19 women: nine women showed no abnormality, seven had generalized atrophy, one had cerebellar atrophy, one had a pineal cyst, and the scan of one suggested encephalitis (normal CSF).

All twenty women had an efavirenz plasma concentration result. The median duration from the last reported efavirenz dose to the blood draw for efavirenz concentration was 19.0 hours (IQR: 17.0–40). Fifteen women's serum efavirenz concentration (including two women taking rifampin-containing TB treatment) was greater than 20mg/L, the limit of detection of the assay; and no efavirenz concentration result was in the therapeutic range. In the single patient with ataxia in the presence of nystagmus who initially was diagnosed with phenytoin toxicity, co-existent efavirenz toxicity was suspected only when ataxia persisted despite resolution of nystagmus. In this patient, repeat phenytoin concentrations were below therapeutic range. Her efavirenz concentration, however, was supra-therapeutic, and her symptoms resolved after withdrawal of efavirenz, suggesting efavirenz toxicity as an additional cause for this patient's ataxia.

Only 10 cases were suspected as having efavirenz toxicity on their first admission; the others had been clinically reviewed 2–4 times prior to diagnosis. Most women were switched from efavirenz to a lopinavir/ritonavir based antiretroviral therapy regimen. Two women had recurrence of ataxia when efavirenz was restarted, one when efavirenz 600mg daily was inadvertently reintroduced at a local clinic, and another when the patient was rechallenged with antiretroviral therapy containing a daily dose of efavirenz 400mg (her repeat efavirenz concentration was >20mg/L); both recovered when efavirenz was withdrawn. One woman had a successful efavirenz rechallenge at daily dose of 400mg. Three patients died. One with neuroleptic malignant syndrome that occurred after introduction of risperidone, the other was not virologically suppressed, had a CD4 of 70 cells/mm³ and passed away at home 2 weeks after being discharged. The third patient died 2 months after discharge with a poorly defined cause of death.

DISCUSSION

We describe a case series of 20 HIV-infected women on ART who presented with efavirenz-induced ataxia and encephalopathy, apparently caused by supra-therapeutic efavirenz concentrations. The ataxia and encephalopathy developed after a median of 2 years on efavirenz, and was reversed once efavirenz was withdrawn. Ataxia was so severe that several patients were unable to walk and/or sit unaided. High concentrations of efavirenz, resolution of symptoms after its withdrawal, and recurrence of ataxia on rechallenge with efavirenz in two patients strongly suggests efavirenz as the most likely cause of symptoms. Prior to diagnosis of efavirenz toxicity several patients had been admitted previously, suggesting clinicians were not aware of this diagnosis.

The 20 patients with this syndrome were diagnosed over 20 months in a single centre suggesting that late efavirenz induced ataxia and encephalopathy is under-recognised. Dizziness and occasional ataxia are common early efavirenz neuropsychiatric side effects, which typically resolve spontaneously within weeks despite continuing efavirenz⁸. However, ataxia has rarely been reported as a late manifestation of efavirenz neurotoxicity, as occurred in our case series. There are isolated case reports of late ataxia due to efavirenz in children and one case report of an adult with fatal encephalopathy and ataxia, who had vacuolar axonopathy involving the brain at autopsy.^{9–11}

The ataxia and encephalopathy we observed was related to high efavirenz concentrations, and, as 12 of our cases weighed less than 40 kg, they should have been prescribed lower doses of efavirenz¹². However, all received a fixed dose combination tablet (FDC) containing efavirenz 600mg daily. FDCs are convenient for public health programmes and improve adherence, but hamper individualization of therapy. In a study of long term efavirenz neuropsychiatric toxicity body weight < 60kg and higher efavirenz concentrations increased the risk of experiencing CNS toxicity¹³. Moreover, it appears recent weight loss possibly due to efavirenx toxicity, may further exacerbate toxicity¹².

The cases we described are likely to be genetic slow metabolizers of efavirenz as their efavirenz concentrations were extremely high. Efavirenz is primarily metabolised by the cytochrome P450 (CYP) isoenzyme 2B6. Several loss of function single nucleotide polymorphisms in *CYP2B6* have been identified, leading to high efavirenz concentrations, which increases risks of toxicity^{14–16}. Toxicities related to efavirenz concentrations, like the ataxia and encephalopathy we describe here, occur more commonly in populations with a high prevalence of *CYP2B6* slow metabolizer genotypes, like sub-Saharan Africa and India^{17,18}. Individuals on efavirenz who are underweight or slow metabolizers of efavirenz are at a higher risk of developing severe ataxia and encephalopathy with chronic exposure to high concentrations of efavirenz. It may therefore be appropriate for those countries using efavirenz as their antiretroviral regimen backbone to make therapeutic drug monitoring for efavirenz available when suspicion of toxicities exists, or when patients are co-treated with inhibitors or stimulators of P450 enzyme¹⁹.

This is a case series and the conclusions that can be drawn from it are limited. There is no control group, so we are unable to comment on risk for this condition. All cases were women, so our findings may not apply to men. Patients were diagnosed by internists and were not evaluated in a standardized fashion by a neurologist or psychiatrist, nor were detailed psychiatric or psychometric tests were undertaken. Finally we did not ascertain efavirenz metabolizer genotype.

We describe a clinical syndrome of ataxia and encephalopathy due to high concentrations of efavirenz in underweight women on long-term ART. The toxicity was severe, but reversible after withdrawal of efavirenz. Future research should determine the incidence of this condition and explore associations with slow metaboliser genotypes. In the interim, we propose that patients on efavirenz presenting with cerebellar ataxia or encephalopathy should have efavirenz concentrations measured immediately, but in settings where efavirenz concentration assays are unavailable, efavirenz should be withdrawn.

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