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ABSENCE SEIZURES ASSOCIATED WITH EFAVIRENZ INITIATION

Renate Strehlau, MB BCh^{*}, Leigh Martens, MB BCh^{*}, Ashraf Coovadia, MB BCh^{*}, Collet Dandara, PhD[†], Jennifer Norman, MSc[‡], Julia Maisel, MB BCh^{*}, Louise Kuhn, PhD^{§,¶}, and Elaine J. Abrams, MD^{||}

^{*}Empilweni Services and Research Unit (ESRU), Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa

[†]Division of Human Genetics, University of Cape Town, Cape Town, South Africa

[‡]Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

[§]Gertrude H. Sergievsky Center, College of Physicians and Surgeons, New York, NY

[¶]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY

^{||}International Center for AIDS Care and Treatment Programs, Mailman School of Public Health, Columbia University, New York, NY

Abstract

Efavirenz, used in treating pediatric human immunodeficiency virus infection, has central nervous system side effects. We report on a 5-year-old girl with perinatally acquired human immunodeficiency virus infection, presenting with new onset absence seizures after starting treatment with efavirenz. Plasma efavirenz values were above therapeutic range. The child was homozygous for the CYP2B6–516T/T genotype, which is associated with poor efavirenz clearance. Seizures abated after efavirenz discontinuation.

Keywords

new onset; absence seizures; efavirenz

Efavirenz (EFV) is widely used as a component of triple antiretroviral (ARV) drug regimens in the management of pediatric human immunodeficiency virus (HIV) infection. Central nervous system (CNS) side effects have been reported in relation to its use.¹ We report the case of a 5-year-old girl with perinatally acquired HIV infection who presented with new onset absence seizures 1 month after EFV was added to her ARV drug regimen.

CASE REPORT

A 4-year 7-month-old black South African female with perinatal HIV-1 infection presented with absence seizures and behavioral changes 1 month after changing her ARV regimen to include EFV.

The child was diagnosed with HIV-1 infection by qualitative DNA PCR at 52 days of life. Her CD4% was 25.9 (cell count 688 cells/mm³) at diagnosis. At 4 months of age, HIV RNA viral load was >3 million copies/mL (Roche Amplicor Assay Version 1.5, Branchburg, New Jersey) and a twice daily ARV regimen, including a boosted protease-inhibitor (PI) (lopinavir/ritonavir—LPV/r, 230 mg/m² of LPV component q 12 hours) and 2 nucleoside reverse transcriptase inhibitors (lamivudine, 4 mg/kg q 12 hours and stavudine, 1 mg/kg q 12 hours), was initiated.

The child was maintained on the PI regimen with a robust immune response and persistently undetectable HIV RNA titers. At 4-year 6 months of age, she was enrolled into a clinical trial investigating treatment options for PI-treated children (clinicaltrials.gov NCT01146873). At enrollment, CD4% was 53.4 (2359 cells/mm³) and HIV RNA viral load was <20 copies/mL. The child was randomized to substitute EFV (300 mg od), a non-nucleoside reverse transcriptase inhibitor, for LPV/r, while continuing the nucleoside reverse transcription inhibitors.

At the 1-month postrandomization visit, the mother reported that the child was experiencing staring episodes from which she could not be roused. The episodes occurred 2 to 3 times daily, lasted less than 1 minute, and were reported to have started approximately 2 weeks after the drug substitution. No associated abnormal behaviors such as eye blinking or lip smacking were noticed. There was no prior history of seizures, and a family history of seizure disorders was negative. The child was taking daily multivitamin syrup; use of traditional medications or other drugs was denied.

No gross abnormalities were noted on systemic or neurologic examination. However, the child's behavior appeared to be subdued. An otherwise happy, active, and outgoing child sat quietly on the examination couch. During the examination, the child was noted to be staring and unresponsive when her name was called. The episode lasted less than 1 minute and the child did not display any postictal drowsiness.

An EEG was performed during which the child was hyperventilated to induce seizure activity. The resultant brain wave activity showed generalized bursts of high amplitude slow waves as well as generalized polyspikes, consistent with seizure activity. Childhood absence epilepsy is typically identified with 3-Hz generalized spike and wave discharge and normal-for-age background wave pattern on EEG.

As EFV toxicity was considered a possible cause of the seizure activity and behavior change, the plasma EFV concentration was evaluated and genotyping for CYP2B6 516G > T single nucleotide polymorphism was done. Mid-dose plasma EFV value (taken 15 hours after the last dose) was 19.62 µg/mL (reference range, 1–4 µg/mL).² Genotyping showed that the child was homozygous for the CYP2B6–516T/T genotype, which is associated with severely reduced CYP2B6 activity, and therefore reduced EFV clearance causing greater EFV plasma exposure.³

EFV was discontinued and LPV/r restarted. One month after the medication change, the staring spells had abated and the child resumed her normal affect. Repeat EEG done 2 months after discontinuing EFV did not show any seizure activity.

DISCUSSION

EFV was approved by the Food and Drug Administration in 1998 for use in combination with other ARVs for the treatment of HIV-1 infection in adults and children ≥3 years. EFV dosing, safety, and efficacy in younger children and those weighing <10 kg, has not been established. The South African Pediatric HIV Treatment Guidelines recommend EFV as part

of the first-line regimen for children ≥ 3 years of age.⁴ World Health Organization guidelines recommend dosing EFV capsules or tablets according to weight, 15 mg/kg/d once daily for children and 600 mg once daily for patients >40 kg.⁵

EFV is primarily metabolized by cytochrome (CYP) P450 isoenzymes 2B6 and to a lesser extent by CYP2A6, CYP3A4/5, CYP1A2, and UGT2B7⁶ to inactive hydroxylated metabolites in the liver.⁷ Genetic polymorphism is associated with variable levels of CYP2B6 expression⁸ and thus EFV metabolism is dependent, on CYP2B6 activity. A common single nucleotide polymorphism, with a base change at position 516 from G to T (CYP2B6-516G > T), is associated with reduced EFV metabolism resulting in elevated plasma EFV concentrations.⁹ Homozygous CYP2B6-516T/T carriers can have substantially higher EFV plasma values compared with CYP2B6-516G/G homozygotes.³ The CYP2B6-516T allelic variant is more common in African populations with a reported prevalence of 36% to 60% in adult populations.¹⁰

Though not as extensively studied in children, similar findings have been reported. Saitoh et al¹¹ reported the median oral clearance rate of EFV was significantly lower in children with the CYP2B6-516T/T genotype than in children with either the G/T or the G/G genotype. Drug pharmacogenetics in children is also affected by physiological changes in growth and development as well as immature enzyme systems and clearance mechanisms.¹² Also of note for children are recent reports that recommended dosing guidelines do not necessarily achieve optimal EFV concentrations. In the study by Ren et al,¹³ 6 (40%) of 15 HIV-infected children receiving the recommended EFV dose had estimated C_{min} values lower than the recommended therapeutic concentration. Resultant low EFV concentrations can lead to the emergence of resistant drug mutations and possible treatment failure.

EFV has been associated with CNS toxicity, with 20% to 40% of adults reporting CNS symptoms or neuropsychiatric adverse events,¹⁴ including dizziness, nightmares, insomnia, mood changes, and less frequently, more severe psychiatric symptoms such as depression, suicidal ideation, and psychosis.¹⁵ Similar findings have been reported in children, but appear to be less common. The few studies that have reported adverse CNS events in children, report an incidence ranging from 14% to 30%.^{16,17} CNS-related adverse events usually diminish within the first few weeks of treatment,¹⁸ but treatment discontinuation or drug substitution may be required for persistent or severe toxicities.

There are conflicting findings regarding the relationship between CNS adverse events and plasma EFV values in adult populations. Several studies have shown higher rates of CNS side effects among patients with high plasma EFV values,^{19,20} while others have been unable to confirm this finding.²¹ Fewer studies have been conducted in children. In 1 study of 27 children receiving EFV, 8 (24%) reported CNS-related toxicities with a nonsignificant trend toward higher EFV levels among those reporting adverse events.²² Another pediatric study found no significant relationship between EFV plasma values and CNS adverse events.²³ However, in the study of 63 Thai children, there was a strong correlation between psychiatric toxicities (4 depression, 1 psychosis) and EFV plasma concentrations.¹⁷

Two cases of seizure activity associated with EFV use in children have previously been reported. A 10-year-old girl, with a family history of epilepsy, had a single generalized seizure 6 weeks after EFV was substituted for a PI in her ART regimen. ARVs were not interrupted, nor were antiepileptics started and no further seizure activity was reported.¹⁶ Wintergerst reported seizure as an adverse event in one of 33 children enrolled in an EFV pharmacokinetic study but no details of the case were provided.²² In addition, a 12-year-old white female developed acute psychosis attributed to a very high plasma EFV level (19,013

ng/mL), which resolved after EFV was discontinued.²⁴ We believe that this is the first report of absence seizures associated with elevated EFV plasma values in a child.

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