CLINICAL ALERT
Efavirenz as a cause of ataxia in children

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Acute ataxia in childhood is often caused by toxin ingestion. With the increasing number of paediatric patients on antiretroviral medication, we are seeing more side-effects of these drugs. We report two cases of efavirenz toxicity causing ataxia.

A child presenting with ataxia may pose a diagnostic dilemma. After excluding the common causes, including toxins, infection and tumours, one needs to look carefully for a possible genetic cause. With limited genetic testing available in South Africa (SA), a definitive answer is not always found.

It is estimated that there are 360 000 HIV-positive children under 15 years of age in SA,[1] 44% of whom are on antiretroviral therapy (ART).[2] These young patients often pose unique diagnostic challenges. We highlight an important differential to consider in HIV-positive paediatric patients presenting with ataxia.

Case reports
Case 1
A 6-year-old girl presented with an acute onset of confusion, vomiting and difficulty in walking. She was HIV-positive and had been on ART for the past year. She was on the standard first-line regimen comprising abacavir, lamivudine and efavirenz (EFV), each of which was dosed appropriately according to her weight and the Southern African HIV Clinicians Society guidelines. Her viral load a month before admission had been <100 RNA copies/mL and her CD4 count was 250 cells/μL. There was no history of toxin ingestion.

On examination she was markedly ataxic and unable to walk or sit unsupported. She was also noted to have titubation, dysmetria and dysdiadochokinesis.

Investigations for a possible infectious cause were undertaken. The findings on lumbar puncture (LP) were normal and serological investigations for varicella virus were negative. However, a computed tomography brain scan was suggestive of possible inflammation of the cerebellum ('cerebellitis'). Magnetic resonance imaging (MRI) of the brain, to better delineate the posterior fossa structures, revealed a normal brain.

While the signs of cerebellar dysfunction had started acutely, their continuation for more than 2 weeks prompted further investigation for an inherited cause of progressive chronic ataxia (our differential diagnosis included ataxia telangiectasia (no telangiectasia were present clinically and the immunoglobulin levels were normal), abetalipoproteinaemia, Friedreich's ataxia and spinocerebellar ataxia. Genetic testing was negative.

The vomiting, with the persistent ataxia, led to consideration of possible medication toxicity. The EFV level was 69 110 ng/mL (v. reference 1 000 ng/mL as the minimum target trough concentration). On stopping the EFV, the patient showed signs of clinical improvement with resolution of vomiting and ataxia. A protease inhibitor was not started at this time as the elevated EFV levels were expected to act as the third antiretroviral agent.

A repeat EFV level done 7 days after stopping the drug showed persistently high levels (49 000 ng/mL), but the patient was able to walk unsupported and the dysmetria and dysdidadokinesia had improved. The decision was made to change the patient to lopinavir/ritonavir, and a month after stopping the EFV she showed no residual cerebellar signs.

Case 2
A 13-year-old girl was referred to the paediatric neurology clinic at Chris Hani Baragwanath Academic Hopsital, Johannesburg, SA, with an acute onset of ataxic gait. She had been diagnosed with HIV infection 3 years previously and staged as World Health Organization clinical stage IV, but was only started on ART (abacavir, lamivudine and EFV) 18 months before her referral. The doses were all appropriate for weight according to the Southern African HIV Clinicians Society guidelines. She was virally suppressed, with an HIV viral load of 28 RNA copies/mL and a CD4 count of 554 cells/μL.

On examination she had a broad-based ataxic gait. Other cerebellar signs included dysmetria, dysdiadochokinesis and mild staccato speech, but no nystagmus.

Initial investigations were done to look for a possible infective cause. The findings on LP were normal, and serological investigations for varicella were negative. An MRI scan of the brain showed no intracranial lesions, structural changes or features of infection.

Before investigating further, and on the basis of experience in case 1, we looked for possible EFV toxicity. The level was 16 274 ng/mL.

Three weeks after stopping the drug, and relying on the elevated EFV levels to continue to act as the third antiretroviral agent, the EFV level had dropped to 1 002 ng/mL with clinical improvement in the patient's gait and resolution of her dysmetria. It was decided to opt for lopinavir/ritonavir as her third antiretroviral agent, and EFV was discontinued.

EFV drug level methodology
EFV is administered as a once-daily dose given at night to limit side-effects, and blood samples for measurement of steady-state drug

levels were collected from our patients during the day before 12h00. Samples were collected in a 5 mL heparinised BD Vacutainer vial (BD Plymouth PL6 7BP, UK) and stored at 2 - 8°C until analysed. Analysis was performed using liquid chromatography-tandem mass spectrometry (LC-MS MS) at Ampath Laboratory in Johannesburg. An LC-MS MS TQD (triple quad detector) instrument from Waters in electrospray positive ionisation mode was used, employing an external standard from ChromSystems (6PLUS1 Multilevel Plasma Calibrator Set Anti-HIV Drugs) for quantification. EFV is identified according to its molecular mass of parent ion 316 as well as one daughter ion of molecular mass 244 and retention time.

Discussion

Acute ataxia is defined as unsteadiness of walking or of fine motor movement with a duration of <72 hours. The most common causes are post-infectious acute cerebellar ataxia, toxin ingestion and Guillain-Barré syndrome.[3] However, the possibility of a mass lesion must always be excluded.

The reported prevalence of neurological abnormalities in HIV-positive children ranges from 10% to 68%.[4] An SA study found the prevalence of neurological complications to be 59%, the most common being HIV encephalopathy and long-tract motor signs; however, no cases of cerebellar dysfunction were documented in that study.[4] The occurrence of ataxia in an HIV-positive individual is rare, with the chronic sequelae being neurocognitive impairment and polyneuropathy.[5]

Ataxia in the setting of HIV is generally secondary to an infectious, vascular or neoplastic cerebellar lesion. Most infections are opportunistic and unlikely to occur in the setting of a sufficient CD4 count.[5] Vascular or mass lesions are readily excluded with neuroimaging.

EFV is a non-nucleoside reverse transcriptase inhibitor that disrupts HIV replication by inhibiting the reverse transcriptase enzyme. EFV is known to have good central nervous system (CNS) penetration,[6] and owing to its long half-life is administered as a once-daily dose. EFV forms part of the SA first-line ART regimen for children >3 years of age and >10 kg in weight.[7]

CNS symptoms are the most frequently reported side-effects in HIV-positive patients on EFV, and include dizziness, headache, confusion, stupor, impaired concentration, agitation, amnesia, depersonalisation, hallucinations, insomnia and strange dreams.[6,8-14] The frequency of CNS side-effects is estimated to be 20 - 40%.[10] The majority of patients who develop CNS and psychiatric adverse effects do so in the first 6 weeks of treatment,[11] with most symptoms resolving by 6 - 10 weeks after treatment initiation.[6] One article documented neurocerebellar side-effects – self-reported dizziness, ataxia, insomnia, bad dreams and hallucinations, without objective assessment of ataxia – in patients using EFV, occurring most frequently in the first month after initiating EFV and declining with time.[12]

Many studies have looked at the effect of the EFV drug level on the frequency of side-effects. Marzolini et al.[10] reported a 24% increase in CNS side-effects if the plasma level was >4 000 ng/mL. However, other researchers have found no correlation between adverse effects and plasma concentrations.[8,9] Gutierrez et al.[13] nevertheless found that CNS side-effects associated with long-term EFV administration were related to plasma levels.

Wide variations in the plasma levels of patients on the same weight-appropriate dose of EFV have been demonstrated. One factor attributing to this individual variation in levels is polymorphism of the CYP2B6 enzyme on cytochrome P450, as EFV is a substrate of this enzyme.[9] The prevalence of the slow-metabolising genotype was 30% in a Botswana study, and other studies have also shown a relatively higher incidence of this genotype in African populations.[14]

Conclusion

Ataxia in both our patients was attributable to the high plasma concentration of EFV, which was at least four times greater than the toxic level (4 000 ng/mL) described by Marzolini et al.[10] and improved when the drug was discontinued. Polymorphism of the CYP2B6 enzyme may explain the very high plasma levels seen.

When a child known to be on EFV presents with acute progressive ataxia, after excluding the common causes, the EFV plasma levels should be checked; if they are toxic, stopping the agent and substituting it with an alternative class of antiretroviral drug should be considered.

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