Case Report

Infection or drug toxicity? Acute ataxia and encephalopathy after uncomplicated falciparum malaria and efavirenz dose adjustment

William P. Brasher[1,2], Menard Bvumbwe[2], Peter N. Kazembe[2]

1. Baylor College of Medicine, Houston, TX, USA
2. Baylor College of Medicine Children's Foundation Malawi, Lilongwe, Malawi

Correspondence: William Brasher; (guillermobrasher@gmail.com)

Abstract

Acute ataxia in children is a rare clinical syndrome usually caused by an infectious, post-infectious, or toxin-related aetiology. Although infrequent, acute ataxia can be related to more common diseases and treatments in Southern African countries including side effects of efavirenz-based anti-retroviral therapy (ART) for HIV or the post-malaria neurologic syndrome (PMNS) after infection with falciparum malaria. We describe a case from Lilongwe, Malawi of a 16-year-old HIV-positive patient with viral load suppression who presented with acute ataxia, confusion, and diplopia. Although he was on efavirenz-based ART for many years, his dose was increased 6 weeks prior, and he was treated for uncomplicated falciparum malaria 5 weeks prior with resolution of symptoms. Studies including cerebrospinal fluid analyses were normal, and he had rapid improvement of symptoms following discontinuation of efavirenz-based ART. Several case series have described supratherapeutic levels of efavirenz leading to acute ataxia as well as the self-limiting PMNS after non-complicated falciparum malaria. Though rare, recognition of efavirenz and PMNS as causes of ataxia is important to inform prompt treatment for HIV patients with acute ataxia in Malawi and other similar settings.

Key Words; Efavirenz, neurotoxicity, ataxia, Malaria, HIV, Malawi, post-malaria neurologic syndrome

Presentation of the case

A 16-year-old HIV-positive WHO stage 1 male on first line anti-retroviral therapy (ART) with zidovudine/lamivudine/efavirenz (AZT/3TC/EFV) presented to the Baylor Center of Excellence in Lilongwe with 3 days of confusion, ataxia, and diplopia. Symptom onset was rapid without a preceding prodrome. The history was gathered from the patient and his mother. Both denied fever, headache, weakness/numbness, seizure, neck stiffness, speech/swallowing difficulties, rash, drug ingestion, or recent traditional medicine use.

Five weeks prior to presentation, he was seen at the clinic with fever, headache, and sore throat. He was found to have tonsillitis and malaria by malaria rapid diagnostic test (MRDT). He was given treatment with artemether/lumefantrine for 3 days and amoxicillin/clavulanic acid for 10 days. All symptoms improved/resolved by the second week of treatment. There were no neurologic signs or symptoms present at time of malaria diagnosis to suggest cerebral malaria. The patient was diagnosed with HIV by vertical transmission 10 years prior, and last viral load was undetectable approximately 2 years prior. He had been taking AZT/3TC/EFV since 2012. He had a recent adjustment from the paediatric dose of 400 mg of efavirenz to the adult dose of 600 mg 6 weeks before presentation due to an increase in his weight past 35 kg. It was confirmed verbally and by pill count that he was taking the appropriate adult dose daily. He was also taking daily isoniazid 300 mg and pyridoxine 25 mg for tuberculosis prophylaxis but not taking trimethoprim/sulfamethoxazole prophylaxis due to allergy.

On exam, he was afebrile with normal pulse rate and blood pressure. He appeared confused with Glasgow Coma Score of 14/15 and was able to answer only some orientation questions. On neurologic exam, his extraocular movements were intact and pupils were equal, round, and reactive to light and accommodation. No vertical or horizontal nystagmus was observed. All other cranial nerves were intact. Cerebellar testing revealed truncal ataxia and dysdiadochokinesia. No dysmetria was observed. Strength was 5/5 in all extremities and sensation was intact. He had a broad-based wobbly gait and was unable to complete a tandem gait.

Clinical course

After a lumbar puncture was done (Table 1), he was hospitalized at Kamuzu Central Hospital (KCH) for 3 days and ART was withheld. He was started on acyclovir for possible HSV encephalitis but only received one dose on day 2 due to nursing administration difficulties. By day 2, he was already improving with normal gait and less confusion, although still complaining of diplopia. By day 3, all symptoms were resolved and he was discharged on a week's course of acyclovir. On follow-up 1 week later, he was started on alternate ART with tenofovir/lamivudine/dolutegravir and was been symptom free at 2 months follow-up.

Discussion of this case

Acute ataxia is generally defined as unsteadiness of gait or fine motor movement for less than 20 hours duration. In children/adolescents, two of the most common causes are post-infectious aetiologies and toxin ingestion [1]. From the history, the most likely aetiologies for our patient include post-malaria neurologic syndrome (PMNS), efavirenz CNS toxicity, or viral encephalitis. Due to lack of fever, leukocytosis, normal cerebrospinal fluid analyses, and normal CD4 count with suppressed viral load (Table 1), a non-infectious aetiology was considered more likely. No toxicology screen was done, but the patient had no history of illicit drug use according to the mother, and there were no

https://dx.doi.org/10.4314/mmj.v32i4.9

Table 1. Diagnostic tests

Full blood count	5 weeks prior	At presentation	Normal range
White blood cell count	11.9	3.6	4–11
% Neutrophils	N/A	40%	45–70%
% Lymphocytes	N/A	51%	20–40%
% Eosinophils	N/A	N/A	1–5%
% Monocytes	N/A	N/A	0.2–0.8%
Haemoglobin (g/dl)	13.3	14.7	11.5–16.5
Platelet count	300	348	150–500
Serum testing			
CD4 cell count (cells/ml)	N/A	550	500–1400
HIV viral load (copies/ml)	N/A	<150	<150 copies
Serum cryptococcal antigen	N/A	Negative	Negative
MRDT	Positive	N/A	Negative
Lumbar puncture			
WBC	N/A	0	0–8
% Neutrophils	N/A	N/A	N/A
% Lymphocytes	N/A	N/A	N/A
Glucose (mg/dl)	N/A	81	50–80
Protein (mg/dl)	N/A	25	15–45
India Ink Stain	N/A	Negative	Negative

other features of lethargy, pupillary abnormalities, or emesis that might suggest marijuana, alcohol, or benzodiazepine ingestion. We will discuss both remaining possibilities of efavirenz toxicity and PMNS as the cause of acute ataxia in our patient.

PMNS is a rare transient condition following recovery from malaria, thought to be an autoimmune phenomenon. The diagnosis requires proven recent malarial infection, clearance of parasite, development of symptoms within 2 months of infection, and ruling out other conditions such as viral encephalitis. Confusion is the most common manifestation in up to 50% of patients, but ataxia has been reported in up to 11% of patients. It can occur anytime between 2 and 30 days following clearance of parasitaemia and reported duration of symptoms ranges from 3 to 25 days [2,3]. Cerebellar manifestations of PMNS are sometimes described separately as delayed cerebellar ataxia (DCA), a self-limiting, usually midline cerebellar ataxia following falciparum malaria. In a large case series of 74 patients diagnosed with DCA from Sri Lanka, all patients presented with predominately truncal ataxia a median 12 days after being diagnosed with malaria. All patients recovered [4]. Other cases have described delayed cerebellar ataxia with detectable parasitaemia immediately after the febrile phase [5]. Our patient's profile fits with a diagnosis of PMNS, sharing more clinical features with patients described as having DCA. Our patient developed confusion and truncal ataxia about 37 days after an uncomplicated case of falciparum malaria and was afebrile with sterile CSF. However, symptoms resolved quicker than usually described.

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) and part of first-line ART in Malawi with high CNS penetration and known dose-dependent neuropsychiatric effects. The most common effects are dizziness, sedation, abnormal dreams, and depressive symptoms that usually resolve after a month of therapy. However, CNS side effects are more likely at high serum concentrations and in genetically slow efavirenz metabolizers [6]. Although current adult dosing is 600 mg daily, generally started at around 35-40 kilograms, a 2014 randomized control trial(ENCORE1) demonstrated that the 400 mg dose is as effective at viral load suppression and associated with less serious definite medication-related adverse events than the 600 mg dose [7]. In addition to the well-known psychiatric effects and sedation, two published case series of patients from South Africa demonstrated a severe reversible acute ataxia associated with supratherapeutic concentrations of efavirenz. The first describes 20 adult women who had been on efavirenz for an average of 2 years, who developed truncal ataxia and encephalopathy. Other causes were ruled out and symptoms improved with lowered dosage or cessation of the drug. They used an assay with a therapeutic range from 1 to 4 mg and 15/20 women had levels above the upper limit of the assay at 20 mg/L. No abnormalities in liver function tests were described that could be detected without drug level testing [8]. The other case series describes two children on efavirenz who also developed symptoms with supratherapeutic levels despite appropriate weight-based dosing [9]. Given our patient's guideline-appropriate adjustment from 400 mg to 600 mg of efavirenz and the onset of symptoms almost identical to those reported in these two case series, efavirenz toxicity seems the most likely cause.

Conclusion

Acute ataxia is rare and is usually related to infection, toxins, or post-infectious autoimmune phenomena. In an HIV-infected patient in Malawi presenting with acute ataxia, efavirenz and PMNS are important diagnoses to consider. Hopefully, the availability of new non-efavirenz-based ART in Malawi will diminish the CNS toxicity some patients experience with efavirenz.

Conflicts of Interest

The authors declare no conflict of interest

References

1. Whelan, H T., Verma S, Guo Y, Thabet F, Bozarth X, Nwosu M, et al. "Evaluation of the child with acute ataxia: a systematic review." Pediatr Neurol. 2013; 49(-1) 15–24.

2. Yadava, S, Laleker, A, Fazili, T. "post-malaria neurological syndrome: a rare neurological complication of malaria." Infection. (2019;47): 183–9.

3. O'Brien, M D., Jagathesan, T, "Lesson of the month 1: post-malaria neurological syndromes." Clin Med (Lond). 2016;-16-(3) : 292–3.

4. Senanayake N, de Silva HJ. Delayed cerebellar ataxia complicating falciparum malaria: a clinical study of 74 patients. J Neurol. 1994;241:456–9.

5. Sakaria, A K, Mahajan SK, Desai RR, Shah KB. "Delayed cerebellar ataxia: a rare self limiting Complication of Plasmodium Falciparum Malaria." Adv Biomed Res 2013;2(27): 27.

6. Haas, W, Ribaudo HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM et al. "Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study." AIDS 2004;18-(18) 2391–400.

https://dx.doi.org/10.4314/mmj.v32i4.9

7. Encore1 Study Group. "Efficacy of 400 Mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomized, double-blind, placebo-controlled, non-inferiority trial." Lancet 2014. 2014; 383(-.9927): 1474–82.

8. Variava E, Sigauke FR, Norman J, Rakgokong M, Muchichwa P, Mochan A, et al. "Brief report: late efavirenz-induced ataxia and encephalopathy: a case series." Acquir Immune Defic Syndr. 2017; 75(-.5): 577–9.

9. Hauptfleisch, M.P.K., Moore, D.P., Rodda, J.L. "Efavirenz as a cause of ataxia in children" S. Afr Med J. 2015; 105-(10): 876.

https://dx.doi.org/10.4314/mmj.v32i4.9