Late Efavirenz-induced Ataxia and Encephalopathy. A Case Series

Ebrahim Variava

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Introduction

- Guidelines in LMIC recommend efavirenz based ART as FDC
- Dolutegravir replacing efavirenz in high income countries
- We describe women , on efavirenz for a prolonged period presenting with:
  - **Ataxia,**
  - **Encephalopathy,**
  - **Underweight,**
  - **Toxic efavirenz concentrations**
  - **Recovery on efavirenz withdrawal**
  - **Recurrence with reintroduction of efavirenz**

Methods

- Had seen a number of cases presenting with ataxia and episodic encephalopathy without a clear cause.

- Case histories of patients investigated by Internal Medicine Dept; Jan 2015-Aug 2016.
- Reviewed:
  - clinical notes
  - weight
  - lab results
  - radiological investigations
  - Efavirenz concentration (UCT)-stored and batched

- Investigated for common causes of ataxia and encephalopathy

Other causes of ataxia-encephalopathy excluded

- **Intracranial pathology**: CSF, CT/MRI Scan
- **Metabolic**: TSH, Chemistry
- **Infectious:** Lumbar puncture
- **Neoplastic**: Chest X-ray
- **Familial**: History
- **Medications**: Anti-epileptics,
- **Illicit** drugs/alcohol
- **Nutritional**: Vits: B12 and B1

Results

All were African women

All were receiving FDC: 600mg efavirenz

Base Line Profile	(IQR)
Age Median	30.5 yrs (24-36)
Duration of ART(Months)	24 mth (12-66)
Weight	37.9 kg (34.1-42.6)
Median CD4 cell count	330 cells /mm^3 (244-547)
Viral Suppression	17 pts suppressed, 1 unsuppressed.
Previous admissions within last 6 months	1 x 3 admissions 3 x 2 admissions 4 x 1 admission

Clinical History and Exam

Psychiatric symptoms or hx of psychiatric event at some point	20 pts
Acute Psychosis	9
Delirium	4
Mood disorder	2
schizophrenia	1
Seizure	1
None	3

Con meds	14 pts
Phenytoin	1
Valproic acid	3
Amytryptoline	2
SSRI	2
benzodiazepine	1
Haleperidol/risperdone	3
Antihypertensives	1
Pyridoxine	2
INH-prophylaxis	1
Rifampin based TB trx	2

Ataxia	
Truncal severe	11
Limb	5
combined	4

Nystagmus	
Absent	19
present	1 (phenytoin toxic)

Stacato speech	
present	15
Abscent	5

Duration of ART	Median (IQR)
Median duration of ART prior to presentation	2 yrs (1-5.5 yrs)

Investigations

"Routine tests"	N=20
Hb (normal)	**14**
Microcytic Fe Def	1
Macrocytic anemia	1
Normochromic Normocytic	3
Bicytopenia (low wcc low plat)	1
AKI	2
CMP normal	**15**
hypophosphotemia	1
LFT- normal	**13**
ALP/GGT increase	3
Cholestatsic	1
Hepatitis (viral serology neg)	1

Investigations	20
CSF	Negative in all
B12/TSHRPR	All normal values
RPR	Negative
Phenytoin level	Done twice on same pt 2-same 1st -toxic and 2nd sub therapeutic
Valproate level	1 (normal)

imaging	20Pts
CXR normal	**15**
infiltrates	2
bronchiectasis	2
Sonar (7 pts) normal	**6**
Echogenic kidney	1
CT Brain	**20**
normal Generalised atrophy	10 (50%) 9 (45%)
Isolated cerebellar atrophy	1(5%)
Pineal cyst	1
MRI	**2**
Cerebellar atrophy	1
encephalitis	1

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Efavirenz concentration	20 pts
>20mg/L	15
10-20mg/L	3
5-10mg/L	2
Median time to collection	19hours (17-40)

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Treatment and Outcome

Alternative to standarded efavirenz dose used	Patients
Lop/rit	15
rilpivirine	1
Atz/rit	1
Tdf/FTC	1 (added Lop/rit later)
Reduced efv dose of 400mg	2

Outcome	Patients
Death(causes)	**3**
Neuroleptic Malignant Hyperthermia	1
2 weeks post discharge –virally unsuppressed	1
2 months post discharge-(clinical improvement)	1
Fully Recovery of ataxia	**17**
Median weight gain in those with weights 6-12 months (IQR)	7/8 demonstrated wt gain 10,8(8-11)
Time to Recovery	2 months (1.25-4)
Re challenge	1 –accidental 2 reduced dose
Recurrence	**2 (1- reduced dose- level >20**
	1 –accidental 1-reduced dose (level >20)

Conclusions

- Case series of 20 women with encephalopathy, ataxia (without nystagmus) virally suppressed, and CD4 response BUT with toxic levels of efavirenz,
- High index of suspicion warranted: neuropsychiatric manifestation related to efavirenz
- All likely slow metabolisers of *CYP2B6* polymorphisms: 17-20% of population. –number exposed?
- Efavirenz Ataxia Toxic Syndrome (EATS)
- Treat EATS: Consider: stop efavirenz immediately; efavirenz levels; switch to either another NNRTI, PI or INSTI.
- FDC low dose efavirenz (400mg).

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