

Cycloserine Induced Late Onset Psychosis and Ethambutol Induced Peripheral Neuropathy Associated with MDR-TB Treatment in an Indian Patient- A Rare Case Report

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ABSTRACT

Adverse reactions and toxicity inevitably accompany all treatment courses for drug-resistant TB. Our case underscores the importance of awareness regarding neuropsychiatric adverse reactions due to MDR-TB therapy and reversible nature of it. Cycloserine induced psychosis is most life threatening complication and sometimes could be fatal. A 42-year-old male on MDR-TB therapy got admitted for his persistent psychotic complaints like hallucinations, delusions and suicidal ideations, despite being treated with quetiapine/olanzapine. Eventually patient was rehabilitated, cycloserine was stopped and psychotic events regressed slowly. Other culprit drugs like ethambutol and levofloxacin causing psychosis was ruled out because there was no relapse of psychotic events despite being continued with these drugs. He also complained of tingling, numbness, swaying, pain and weakness. On examination, he had distal motor weakness in lower limbs, tandem gait positive, altered position sense, and tenderness over toes and positive Romberg's sign with ataxia. He was diagnosed to have drug induced sensorimotor peripheral neuropathy. All these symptoms persisted after stopping cycloserine and patient continued to have neuropathy with ethambutol and ethionamide. Considering the nature of neuropathy which was mild, mixed sensorimotor and resolved completely after 2-3 weeks of stopping, it was more in favour of ethambutol. However, we could not rule out the possibility of ethionamide or (ethionamide + ethambutol) causing neuropathy or both could have accelerated the neurotoxic effects of cycloserine which remained elusive.

Keywords: Accelerated, Ataxia, Reversible, Romberg's sign, Suicidal ideation

CASE REPORT

A 42 year old male, known case of multidrug-resistant tuberculosis (MDR-TB) on treatment presented to the psychiatric department, Manipal in April 2014 with excessive talking, crying, laughing at self, insomnia and constant suicidal ideations. Family history revealed that his sister and brother were diagnosed with bipolar disorder and depression respectively and currently on treatment. Past history suggested that in 2010, he was diagnosed with pulmonary TB and advised anti-TB regime and asked to be strictly adherent. However, patient was non-compliant and neglected his disease status despite his progressive detrimental health conditions. He was diagnosed as a case of TB treatment defaulter in July 2012 and subsequently DST (Drug Susceptibility Testing) was done to confirm

MDR-TB (*Tubercle bacilli* was found to be resistant to both isoniazid and rifampicin). Treatment for MDR-TB was started immediately by the government hospital under supervision. In January 2014, he developed psychomimetic symptoms for which he was treated by a local doctor with quetiapine initially and changed later to olanzapine and advised not to quit MDR-TB therapy [Table/Fig-1].

His personal history as described by his relatives as an introvert, non-smoker and occasional alcoholic. Despite being treated with olanzapine, his condition worsened and his relative brought him complaining his violent behaviour. He was admitted and on clinical examination he was found to be unstable, aggressive, irritable, talking to self, restless, showed frequent mood swings, more fearful, socially withdrawn, and had distorted speech, verbally abusive

Drugs (oral)	Dose/day	15/7/12	15/1/13	5/1/14	25/5/14	18/7/14
levofloxacin(Lfx)	1g	Started	Continued	Continued	Continued	Completed
kanamycin (K)	1000mg	Started	Completed	--	--	--
ethionamide (Eto)	750mg	Started	Continued	Continued	Continued	Completed
pyrazinamide (Z)	2g	Started	Completed	--	--	--
ethambutol (E)	2g	Started	Continued	Continued	Continued	Completed
cycloserine (Cs)	750mg	Started	Continued	Continued	Discontinued	--
pyridoxine	100mg	Started	Continued	Continued	Increased	Continued
quetiapine	25mg	--	--	Started	Stopped	--
olanzapine	20mg	--	--	--	Started	Continued

[Table/Fig-1]: Standard MDR-TB regime according to the revised RNTCP guidelines [1] and other drugs used

towards family members. He had insomnia and felt that somebody was conspiring against him. He continued to have suicidal thoughts (attempted suicide on 2-3 occasions), excessive crying spells and complained of apathy because of burden of medications. He was diagnosed having cycloserine (Cs) induced psychosis and drug was stopped immediately.

He also complained of tingling, numbness in lower limbs, swaying while walking, pain in the lower limbs, severe weakness, ataxia and difficulty in carrying out routine activities like getting up from squatting position. There was no history of blurring of vision, diplopia, nausea and vomiting, headache, difficulty in swallowing. On neurological examination, both sensory and motor modalities were involved wherein, he showed distal motor weakness in both upper and lower limbs, impaired balance, tandem gait, impaired co-ordination and altered position sense. On sensory involvement, slight numbness, tenderness for touch in both lower limbs over toes, poor co-ordination and balance, positive Romberg's sign with ataxia typically of sensory in nature was present. Neurologist inferred that the patient had mixed mild sensorimotor peripheral neuropathy, altered behaviour and gait/postural imbalance.

DISCUSSION

According to the Naranjo's ADR assessment scale cycloserine induced psychosis scored 6 i.e. 'PROBABLE' and ethambutol induced peripheral neuropathy scored 4, i.e. 'POSSIBLE'. Our patient had neither depression nor psychosis until the drugs like cycloserine, ethambutol, ethionamide, levofloxacin were started as MDR-TB therapy. Despite his brother and sister being diagnosed with depression and bipolar disorder respectively, the patient did receive cycloserine because he had no personal history of neuropsychiatric events. Among these medications, cycloserine is very notorious to cause neuropsychiatric symptoms and occur in 50% of patients on 1 g/day [2-4]. Interestingly, our patient was put on tab. cycloserine 750mg/day for many months but hardly ever complained of any problems till January 2014. However, he had inconsistent personality events described by his brother as isolated, highly irritable and depressed or sometimes over reactive but refused consultation. His problems remained unnoticed and uncalled for suggestions. In January 2014, he was treated with quetiapine initially then changed to tab. olanzapine and advised not to quit the MDR-TB therapy. The most offending drug cycloserine was discontinued in May 2014 because severe psychotic symptoms like hallucinations, delusions and suicidal ideations persisted despite therapy with quetiapine and olanzapine [Table/Fig-1].

Recently, psychotic adverse reactions with levofloxacin (Lfx) are also being encountered [5]. Since psychotic features in our patient recovered completely on cycloserine withdrawal, and he was continued on levofloxacin and ethambutol without any recurrence of symptoms, they appear unlikely to be the cause. Considering the onset of psychotic reaction within few months of start of cycloserine and complete remission of symptoms within 30 days of withdrawal, cycloserine was the most likely offending drug in our patient.

Some of the anti-tubercular agents in use may cause peripheral or optic neuropathy. Ethambutol is less neurotoxic but may cause optic neuropathy, a mixed sensorimotor neuropathy, or a predominantly sensory neuropathy [6]. Ethambutol is recognized to cause neuropathy in a dose dependent manner. Ethionamide is structurally related to isoniazid, may rarely cause sensory neuropathy which takes several months to resolve upon discontinuation. The mechanism is speculated to be interference of pyridoxine metabolism [7]. Co-administration of pyridoxine (50-100mg/day) is protective, although excessive doses >200mg/day can cause peripheral neuropathy especially in individuals with end-stage renal disease [8]. We present a case of mild sensorimotor neuropathy due to either concurrent

administration of ethambutol (E) or/and ethionamide (Eto) or it may be a case of exacerbation of neurotoxic effects of cycloserine due to concomitant administration of E+ Eto+ Lfx.

The drugs most commonly implicated are isoniazid, ethionamide, cycloserine, and linezolid. Fluoroquinolones and ethambutol have rarely been associated with the development of neuropathy [8]. The extensive literature survey has revealed that very few previous published case reports of ethambutol or ethionamide alone or in combination induced peripheral neuropathy in India. However, there were three clinical reports in 1971 suggestive of ethambutol induced neuropathy at the dose range of 20– 50 mg/kg/day. In this case series one case had succumbed with mild sensory and two had developed moderate-severe sensorimotor neuropathy [9]. One patient in 1976 developed both peripheral neuropathy and ocular toxicity while receiving ethambutol in a dose of 20 mg/kg of body weight daily. It is interesting to note that symptoms of peripheral neuropathy preceded the visual disturbance by seven months. Also of note is the fact that she had received ethambutol previously without untoward side effects [10].

Donomae and Yamamoto noted numbness in the legs in seven of their 187 patients who received ethambutol. The authors noted that there was a higher incidence of paraesthesia among those patients who received ethambutol either as a fixed dose of 1 gm daily or 25 mg/kg of body weight per day [10]. Tugwell and James reported peripheral neuropathy in three patients receiving ethambutol in doses of 13 to 50 mg/kg of body weight daily [10]. Schmidt found that in monkeys, high doses of ethambutol caused severe neurotoxic effects resulting in unsteady gait, loss of equilibrium and other disturbances in co-ordination [10]. In an unpublished series collected by Lederle Laboratories of 1024 patients treated with ethambutol, 15 suffered from peripheral neuritis, mainly in the form of numbness of the extremities, at some time during the therapy [9]. Contrary to the above reports, the use of ethambutol in doses of 50 mg/kg of body weight twice weekly up to 78 weeks, in the intermittent therapy of tuberculosis, has not been associated with visual impairment or peripheral neuropathy [10]. In one cohort of MDR-TB case series wherein, peripheral neuropathy was encountered in 10 of 75 patients (13%). Median time to presentation from initiation of MDR-TB therapy was 9.1 months. All patients who developed peripheral neuropathy were diagnosed based on clinical presentation alone and effectively managed without sacrificing MDR-TB treatment efficacy [7].

CONCLUSION

In this era of drug-resistant tuberculosis being rampant especially in resource scarce countries like India, it is very prudent for neurologists and psychiatrists to be aware of neuropsychiatric manifestations of second-line anti-tubercular drugs so that early diagnosis and treatment can improve patient compliance and outcomes. We also suggest that despite the frequency and occasional severity of the neuropsychiatric effects of MDR-TB drugs, aggressive and prolonged treatment is recommended.

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