CASE REPORT

Neuroimaging in Cycloserine Induced Neurotoxicity: A Rare Case Report

Sandeep Sharma[1], Prajay Lunia[1], Unnati Desai[1]*

[1]Department of Pulmonary Medicine, TNMC & BYL Nair Hospital, Mumbai-400008 (Maharashtra) India

Abstract:

Tuberculosis (TB) is an infectious disease. There is an increasing burden of Drug Resistant TB (DR-TB) which is not only difficult to treat and associated with adverse events during its treatment. Cycloserine is a broad spectrum antibiotic used as a second-line agent for DR-TB therapy. Psychiatric adverse drug reactions are well known. Neurotoxicity with the use of supplemental pyridoxine is rarely reported. We report a case of young boy who developed tilting of body to one side during therapy for DR-TB which included cycloserine. Magnetic Resonance Imaging (MRI) of the brain showed reversible bilateral symmetrical (T2/FLAIR) hyperintensity in dentate nuclei. Clinical and MRI findings were consistent with cycloserine toxicity. Symptoms resolved on withdrawing the drug. MRI findings showed marked reversibility.

Keywords: Tuberculosis, Drug Resistant Tuberculosis, Magnetic Resonance Imaging, Cycloserine Toxicity

Introduction:

India is a high burden country for Tuberculosis (TB). The incidence of TB in India is 217 per lakh population as per WHO 2016 report [1]. India accounts for 20 percent of TB cases globally and has reported 30000 Drug Resistant Tuberculosis (DR-TB) cases in 2015 [1]. Cycloserine has been classified by WHO as a second-line Anti-Tuberculosis Therapy (ATT) group C drug, used in a dose of 10-15 mg/kg/day. Adverse effects of cycloserine are mainly dose-related [2]. Psychiatric adverse events such as anxiety, hallucinations, depression, euphoria, behavioral changes and suicidality have been reported in 9.7–50% of individuals while on cycloserine [3]. Hereby, we report a case of extra pulmonary drug resistant tuberculosis presenting with cycloserine-induced neurotoxicity. This case depicts unusual reversible Magnetic Resonance Imaging (MRI) changes of cycloserine toxicity at the dentate nucleus.

Case Report:

A 15 year old boy was brought by his parents to the DR-TB centre follow-up out-patient department, in the month of November 2016, with a new onset symptoms of tilting of body to left side on sitting and walking which increased gradually over one week. There was no history of associated seizures, fever, weakness or any other neurological symptoms. He had previously been treated with empirical ATT for fever, weight loss, dry cough and Chest Roentography (CXR) showing loculated pleural collection, by a private practitioner for 2-3 months. However, his fever persisted, so he was evaluated with diagnostic thoracocentesis and testing of the pleural fluid by Gene Xpert analysis diagnosed Rifampicin Resistant Tuberculosis (RR-TB). The patient was referred to our DR-TB centre and was started on category IV ATT Intensive Phase (IP) in May 2015 which included injection kanamycin (500 mg), tablet levofloxacin (500 mg), tablet ethionamide (500 mg), capsule cycloserine (500 mg) treatment

with tablet pyridoxine (100 mg) supplementation as daily therapy. On therapy, there was defervescence of symptoms and no reported adverse drug events. In October 2015, he was shifted to Continuation Phase (CP) in view of clinico-radiological improvement and kanamycin was stopped. He had completed 19 months of DR-TB therapy till the current presentation with the neurological symptoms mentioned. There was past history of ATT intake in childhood. Currently, on clinical examination the respiratory system was normal. The central nervous system examination was normal for higher functions. There was no sensory or other neurological deficit besides tilting. He tilted to left side on sitting and walking. Patient was evaluated with the finger to finger and finger to nose test, rapid alternating movements of hand, heel to shin test and gait. These cerebellar signs were negative.

His routine hematological and biochemical blood investigations were normal. On evaluation with brain MRI, bilateral symmetrical T2 Weighted Images (T2WI) and Fluid-attenuated Inversion Recovery (FLAIR) hyperintensity in dentate nuclei was reported which appeared isointense on T1 Weighted Images (T1WI), showed no restricted diffusion on Diffusion Weighted Images (DWI)/ decreased Apparent Diffusion Coefficient (ADC) and no blooming on Fast Field Echo (FFE) (Fig.1). Electroencephalography (EEG) was within normal limits and did not show any evidence of epileptiform abnormality. His clinical presentation and MRI findings were proposed to be most consistent with cycloserine neurotoxicity.

Cycloserine was withheld in view of the Serious Adverse Event (SAE). After stopping of the same, the symptoms completely resolved. The follow-up MRI performed 1 month after the discontinuation of cycloserine, showed marked reduction of the high signal intensity in the dentate nuclei (Fig. 2). According to Naranjo causality scale [4], this case scored 5 (2 for adverse reaction after drug was given, 1 for improvement following stopping the drug and 2 for absence of alternative causes). At this time, in view of completion of 20 months of second-line therapy; the patient was evaluated for end of therapy assessment with clinicoradiological correlation. Computed tomography of the thorax showed overall response of the pleural effusion to treatment with residual pleural thickening. He was declared treatment completed and second-line ATT was stopped.

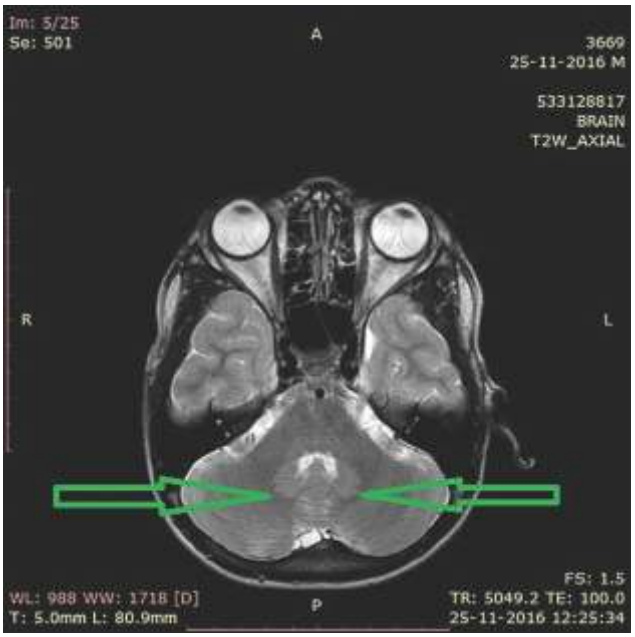

Fig. 1: Magnetic Resonance Imaging (MRI) Brain, Bilateral Symmetrical T2 Weighted Images (T2WI) showing Hyperintensity in Dentate Nuclei (Green Arrow)

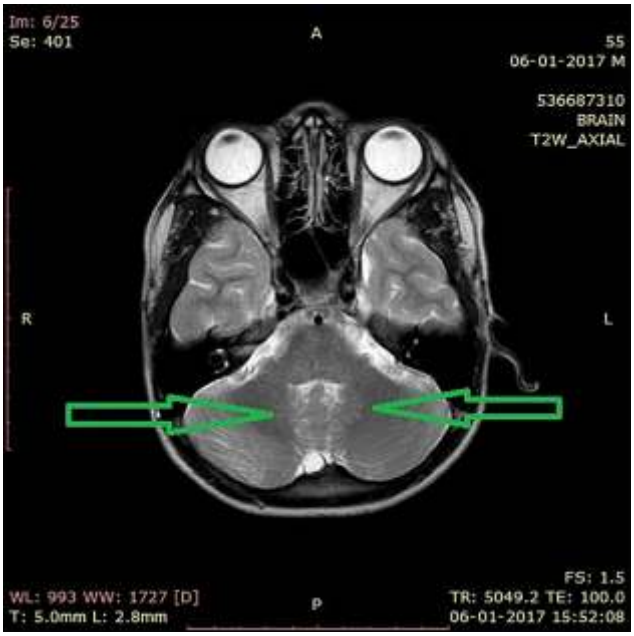

Fig. 2: Post Stopping Cycloserine; Magnetic Resonance Imaging (MRI) brain, bilateral symmetrical T2 Weighted Images (T2WI) showing Marked Reduction in Signal in Dentate Nuclei (Green Arrow).

Discussion:

Cycloserine was first isolated in 1954. It is a broad spectrum antibiotic chemically D-4-amino-3 isoxazolidone [5]. It is a WHO Group C core second line ATT [6]. It acts against crucial enzymes in the cytosolic stage of peptidoglycan synthesis inhibiting cell wall biosynthesis in the mycobacteria [5]. It is a bacteriostatic class of drug [6]. The dosage of cycloserine used in its discovery era was very high (1 gram per day) and severe neuropsychiatric side-effects were noted [5]. In 1969, Cohen AC documented elevated urinary excretion of pyridoxine and hypothesized the adverse events as secondary to its deficiency. They described the use of large doses of pyridoxine for prevention of the neurological SAE [5]. Eventually, the dosage regimen for cycloserine of 10-15 mg/kg/day not exceeding 1 gram/day along with the same doses with supplemental pyridoxine has been recommended by the World Health Organization (WHO) and Revised National TB Control Programme (RNTCP) guidelines [6, 7].

Like other second-line ATT, cycloserine even in lower dosages has been reported to be associated with a spectrum of Adverse Drug Reactions (ADR). Such ADR now described in the product prescribing information included psychiatric side effects such as aggression, bizarre behavior, confusion, depression, disorientation, dizziness, drowsiness, suicidal ideations; neurological effects like headache, vision disturbances, seizures, coma; and rarely skin rashes and allergic reactions. Researchers working with patients being treated for DR-TB have documented 9.1% of patients to have any ADR associated with cycloserine of which 5.7% are psychiatric and 1.1% neurological [8]. Psychiatric ADR associated with cycloserine are often dramatic and serious, and have been exhaustively reported. Often the neurotoxicity coexists with the psychiatric ADR masking the reporting of the same. Isolated neurotoxicity of cycloserine is rarely reported in current literature as national and international guidelines aggressively recommend and implement pyridoxine supplementation [6, 7]. More so, the optimal use of neuroimaging modalities to prove this neurotoxicity is a further rarity.

Previous reports of neuroimaging in cycloserine neurotoxicity have been reported in 2008, 2014 and 2016. Ours is the fourth case report of neuroimaging use for confirming cycloserine toxicity.

In 2008, Kwon *et al*. reported a 69 year old lady, with tuberculous lymphadenopathy on therapy with cycloserine, isoniazid, pyrazinamide and supplemental pyridoxine who developed hypersomnolence and asterixis of one year duration. Brain MRI showed bilateral thalamic hyperintensities on T2WI. Following discontinuation of cycloserine; the patient's symptoms resolved and the repeat MRI showed marked reduction of the high signal intensities in both thalami after one month [9]. In 2014, Kim *et al*. wrote about a 26 year old lady with extensive drug resistant pulmonary tuberculosis on therapy with cycloserine, amikacin, linezolid, levofloxacin, rifabutin and amoxicillin-clavulanic acid without supplemental pyridoxine who developed aphasia, anxiety, dizziness, visual blurring and seizure within a month. MRI with gadolinium showed symmetrical high signal intensity in the dentate nuclei on diffusion weighted images, T2WI, FLAIR and decreased ADC. Following discontinuation of cycloserine; there were no additional seizures or new neurological abnormalities and the MRI showed resolution of high signal intensity in the dentate nuclei after 2 weeks [10]. Subsequently, Jain *et al.* reported a 24 year old Indian lady diagnosed with primary MDR-TB at a tertiary hospital in New Zealand treated with moxifloaxacin, amikacin, prothionamide, Para-aminosalicylic Acid (PAS), cycloserine and supplemental pyridoxine. She presented two months later with labile mood, hypervigilance, daytime somnolence, change in personality, persecutory delusions and suicidal ideations. The brain MRI showed increased signal in the cerebellar hemispheres of dentate nuclei and surrounding white matter on T2WI, diffusion weighted images and decreased apparent diffusion coefficient values. Following cycloserine discontinuation; some symptoms and MRI findings resolved except persistent labile mood [11].

Our patient presented with neurological adverse events with no psychiatric manifestations. He was on optimal pyridoxine supplementation. He had a late onset of these symptoms almost 19 months on therapy i.e. towards the end of therapy unlike the previous cases. This presentation being an unusual one, we first ruled out tuberculous involvement of the central nervous system with a normal neurological examination and MRI showing no evidence of meningitis, hydrocephalus, vasculitis, intracranial tuberculomas or abscess [12]. MRI brain findings were nearly similar to the previously reported cases with the dentate nuclei hyperintensity on T2WI FLAIR, though they were isointense on T1WI and had no abnormality on DWI and ADC. The other conditions included in the differential diagnosis of these MRI findings [13] are leukodystrophies, ischemia and neurodegenerative, demyelinating and inflammatory diseases. None of these were considered as clinically irrelevant. The high clinical suspicion, previous rare reporting of such cases made us to promptly discontinue cycloserine. The clinical abolition of the ADR was consistent with the previous clinical reports. The repeat MRI finding of reduction in the high signal intensities was consistent with the report of 2008 though, they did not completely normalize as in the 2014 and 2016 reports.

Conclusion:

Cycloserine is an important second-line drug for the treatment of DR-TB, though associated with its profile of ADR and SAE. Reversible hyperintensity in the dentate nuclei is advocated

as one of the MRI findings associated with cycloserine neurotoxicity. The prompt use of neuroimaging like brain MRI in such cases can confirm diagnosis of cycloserine adverse effect and help the clinician to take necessary action to prevent mortality and morbidity.

Key message:

Early diagnosis of neurotoxicity due to cycloserine can be made with prompt use of neuroimaging like magnetic resonance imaging of the brain.

References

1. WHO. Tuberculosis country profile-India. https://extranet.who.int/sree/Reports?op=Replet&name=%2FWHO_HQ_Reports%2FG2%2FPROD%2FEXT%2FTBCountryProfile&ISO2=IN&LAN=EN&outtype=html. Date accessed: April 7, 2017.
2. Girling DJ. Adverse effects of antituberculosis drugs. *Drugs* 1982; 23: 56-74.
3. Pachi A, Bratis D, Moussas G, Tselebis A. Psychiatric morbidity and other factors affecting treatment adherence in pulmonary tuberculosis patients. *Tuberc Res Treat* 2013; 2013: 489865.
4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30: 239-45
5. Cohen AC. Pyridoxine in the prevention and treatment of convulsions and neurotoxicity due to cycloserine. *Ann N Y Acad Sci* 1969; 166(1): 346-9.
6. WHO. Multi-drug Resistant Tuberculosis (MDR-TB) 2016 update. http://www.who.int/tb/challenges/mdr/mdr_tb_factsheet.pdf?ua=1. Date last accessed: July 7, 2017.
7. RNTCP PMDT guidelines 2012 RNTCP. Guidelines on programmatic management of drug resistant tuberculosis (PMDT) in India May2012. http://tbcindia.nic.in/showfile.php?lid=3155. Date last accessed: July 17, 2017.
8. Hwang TJ, Wares DF, Jafarov A, Jakubowiak W, Nunn P, Keshavjee S. Safety of cycloserine and terizidone for the treatment of drug-resistant tuberculosis: a meta-analysis. *Int J Tuberc Lung Dis* 2013; 17(10):1257-66.
9. Kwon HM, Kim HK, Cho J, Hong YH, Nam H. Cycloserine-induced encephalopathy: evidence on brain MRI. *Eur J Neurol* 2008; 15: e60-e61.
10. Kim S, Kang M, Cho JH, Choi S. Reversible magnetic resonance imaging findings in cycloserine-induced encephalopathy: A case report. *Neurology Asia* 2014; 19(4): 417-19.
11. Jain M, Lewis C, Moriarty M, Hussain S. Neuropsychiatric toxicity of cycloserine in multidrug-resistant tuberculosis patient with reversible MRI changes. *Am J Respir Crit Care Med* 2016; 193: A3792.
12. Trivedi R, Saksena S, Gupta RK. Magnetic resonance imaging in central nervous system tuberculosis. *Indian J Radiol Imag* 2009; 19(4):256-65.
13. Khadilkar S, Jaggi S, Patel B, Yadav R, Hanagandi P, Fario do Amaral LL. A practical approach to diseases affecting the dentate nuclei. *Clin Radiol* 2016; 71(1): 107-19.

[*]***Author for Correspondence:*** *Dr. Unnati Desai, Department of Pulmonary Medicine, 2nd floor, OPD bldg, TNMC & BYL Nair Hospital, AL Nair Road, Mumbai Central, Mumbai- 400008.*
Email: unnati_desai82@yahoo.co.in, Cell: 02223027643