PAMJ Clinical Medicine
Pan African Medical Journals

Case series

Adverse drug reactions due to cycloserine on the central nervous system in the multidrug-resistant tuberculosis cases: a case series

Sankalp Yadav[1,&], Gautam Rawal[2]

[1]Department of Medicine & TB, Chest Clinic, Moti Nagar, North Delhi Municipal Corporation, New Delhi, India, [2]Respiratory Intensive Care, Max Super Speciality Hospital, Saket, New Delhi, India

[&]Corresponding author: Sankalp Yadav, Department of Medicine & TB, Chest Clinic, Moti Nagar, North Delhi Municipal Corporation, New Delhi, India

Received: 06 Nov 2019 - Accepted: 12 Nov 2019 - Published: 24 Nov 2019

Domain: Internal medicine, Neurology (general)

Keywords: Tuberculosis, cycloserine, central nervous system

Abstract

Cycloserine (CS) is an important part of the tools against multidrug-resistant tuberculosis (MDR-TB). Similar to most of the second line drugs, CS has many adverse drug reactions (ADR). The ADR due to CS related to the central nervous system (CNS) are very rare and are reported in few isolated case reports. We herein, present a first case series from the national capital of India of three MDR-TB patients with CS-induced ADR´s of the CNS. In all the three cases the drug was withdrawn and the symptoms were relieved. The present case series will definitely serve as a tool to spread awareness about the rare ADR´s associated with CS.

Case series | Volume 1, Article 25, 24 Nov 2019 | 10.11604/pamj-cm.2019.1.25.20904

Available online at: https://www.clinical-medicine.panafrican-med-journal.com/content/article/1/25/full

Introduction

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis and is an important public health problem [1-4]. The drug-resistant TB (DR-TB) came to the limelight since 1993 [3]. The DR-TB like multidrug-resistant TB (MDR-TB) involves the use of the second line anti-tubercular treatment (ATT) which are associated with multiple Adverse Drug Reactions (ADR) [5]. The highly toxic drugs, longer treatment duration, pill burden, and ADR are some of the most common reasons for the treatment default [5]. India is a high TB burden country with a rising number of drug-resistant TB cases [5]. The management of such a high load of DR-TB cases in a resource-poor setting leads to a number of issues related to treatment delivery and success. The most common ADR´s due to second-line drugs are commonly treated on an outpatient basis. But the problem arises when the ADR is severe and associated with personality/behavioral change, suicidal/homicidal ideations, depression, etc. Cycloserine (CS) (D-4-amino-3-isoxazolidine) is a very important second-line drug used in the management of the MDR-TB [6]. CS-induced psychosis and other neurological effects are seldom reported in the MDR-TB cases and are available only as sparse case reports in the medical literature [6-9]. Herein we present the very first case series related to CS-induced neurological effects in three MDR-TB cases from the national capital of India.

Methods

We studied three patients belonging to various age groups. All the three cases were under constant monitoring at the OPD basis and were timely evaluated for any adverse drug reactions. The side effects of drugs were carefully evaluated and the stoppage of drugs resulted in a return to normal levels in all the three cases.

Results

A 34-year-old non-diabetic Indian female with a history of being treated for the pulmonary TB (Category I) one year back was brought to the OPD with complaints of weight loss, cough with expectoration, fever with night sweats and loss of appetite since last one month. She was smear positive for acid-fast bacilli (AFB). And thus she was started on Category II pulmonary TB recurrence under the Revised National Tuberculosis Control Program (RNTCP). One sputum sample was sent for Line Probe Assay (LPA) and was found to be resistant to Rifampicin and Isoniazid (R and H). As a result, the patient was switched to a Category IV regimen of RNTCP under the programmatic management of Drug Resistant-TB (DR-TB). After about sixteen days of the Category IV treatment, she developed psychosis with delusions and hallucinations. The family members also reported that the behavior of the patient had changed with aggressive behavior and violent mood swings. She also complained of loss of interest in daily activities, a decrease in sleep, disorientation, and lightheadedness. Since a number of drugs can cause psychotic reactions, thus a provisional diagnosis of drug-induced acute psychosis was made and the patient was referred to the linked Drug Resistant-TB (DR-TB) center for the psychiatric evaluation. After a detailed clinical examination, it was found that the psychosis was attributed to CS and ceased remarkably after two days of withdrawal of the drug. The drug was restarted on the fourth day, but it was noticed that the symptoms returned, thus the CS was withdrawn and again the patient became normal on the third day after the withdrawal of the CS. The withdrawn drug was replaced by Para-Aminosalicylate Sodium (PAS) powder as per her weight.

The second case of 23-year-old Indian male on Category IV ATT due to H and R resistance in the sputum sample sent for LPA came to our OPD with complaints of violent behavior, disorganized speech with irrelevant talk, aggressive behavior

and depressed mood. On detailed history, he was found to have been on Category IV ATT since last one month, including CS (750 mg/day). The patient was counseled by the MDR-TB counselor and the Medical Officer and was referred to the DR-TB site for the detailed clinical evaluation. After detailed examination, CS was stopped considering it to be one of the prime causes for such ADR´s and the results were evident with a return to normalcy after three days of the stoppage of the drug. The third case of 45-year-old Indian male with extra-pulmonary TB involving the right cervical lymph node and with a history of taking ATT twice for the pulmonary TB was found to be extra-pulmonary MDR-TB after CBNAAT examination of the sample collected from the right cervical lymph node. He was found to be resistant to Rifampicin on CBNAAT and the LPA of the sample revealed resistance to H as well. This patient reported to the OPD with complaints of headache, drowsiness, shaking (tremors), bizarre behavior with hearing strange sounds and visual halos, slurred speech and suicidal thoughts. There was delusional jealousy against the spouse. The patient was counseled and referred to the DR-TB site where he was admitted and given anti-psychotics. CS was stopped after detailed examination and this resulted in an improvement in his condition with a return to complete normal levels after four days of the stoppage of the CS. There were no other signs of any neurological deficiency or a history of substance abuse in all three cases. Thus a diagnosis of ADR´s to the CS involving the CNS was made and the offending drug was withdrawn. Written informed consent was obtained from the three patients for the publications of the case details.

Discussion

The ADR´s are commonly associated with the management of the MDR-TB [5]. Drugs such as Isoniazid, CS, Ethambutol, and Flouroquinolones have been reported to produce drug-induced psychosis [10,11]. The published literature suggests that as compared to the other second-line drugs, CS is associated with a higher frequency of psychiatric and CNS-related ADR´s [10-12]. Although the data are limited, and available mostly as isolated case reports, the discontinuation of CS has resulted in complete management of the ADR´s in most of the cases [10]. CS-associated ADR is probably because of diminished central nervous system production of gamma-aminobutyric acid as a result of inhibition of glutamic decarboxylase [13]. We have reported three MDR-TB cases in various age groups with common ADR´s due to CS. To the best knowledge of the authors, this is the first case series of ADR related to CNS due to CS in MDR-TB cases from the national capital of India. In the earlier reports about the ADR´s due to CS, Lewis *et al*. 1957, reported detailed ADR´s in pulmonary TB cases [12]. Sharma *et al*. 2014, reported psychosis, delusions, and hallucinations [7]. Mania was the main presentation in the case by Bakhla *et al*. 2013 [8]. Also, seizure with psychosis was reported by Fujita *et al*. 2008 [9]. Tandon *et al*. reported aggressive and violent behavior, restlessness, anxiety, and insomnia along with severe hepatic dysfunction [6]. Unlike all these well-documented cases, our cases show certain other ADR´s like suicidal ideation, slurred speech, tremors, dizziness, and bizarre behavior. Besides, the present case series differs from the one by Lewis *et al*. 1957, as the three cases presented here are MDR-TB cases [12].

The common side effects of CS are documented elsewhere, but the same in a case series of MDR-TB patients are reported for the first time from the national capital of India. Behera *et al*. 2014, reported a similar case, but even after the withdrawal of the CS the patient committed suicide, thus the role of other drugs such as Ethambutol and Fluoroquinolones that had the potential to cause psychosis in MDR-TB cases need to be studied in detail [11]. The exact mechanism of ADR´s is not known [6]. But the present case series emphasizes the routine counseling and psychiatric evaluation of all the MDR-TB cases on CS [5]. The role of MDR-TB counselors as explained elsewhere is also very important in prompt management of

ADR´s before any major untoward incidence [5]. The MDR-TB treatment involving second-line drugs is a challenge for both the patients and the healthcare providers and thus, the active participation of all the stakeholders like the physicians, TB health visitors, and family members of the patient, MDR-TB counselors, and the DR-TB staff is imperative. Also, in the absence of the detailed reports about the ADR´s due to CS based on large scale studies the role of dissemination of health care information about the CS to all the sections of the society, especially in countries with lean health expenditure is really important and the agencies involved in the dispersal of such information should play an important role [14-16]. The only limitation of this case series was the unavailability of the data of CS levels in the three cases.

Conclusion

The treatment of MDR-TB is long and is associated with a number of ADR´s. The drugs like CS should be carefully administered and such patients should be regularly monitored and followed-up for the psychiatric ADR´s. Any deviation from the normal behavior of a patient on CS should be reported promptly and the expert committee treating such cases should evaluate the risks and benefits before stopping or substituting the drug. Not only this will help in treatment adherence and completion, but this approach will also help in avoiding any untoward incident.

What is known about the topic

- MDR-TB has a long treatment duration;
- Drugs have various adverse effects;
- Treatment is associated with high pill burden.

What this study adds

- The MDR-TB cases Cycloserine should be considered as one of the reasons for psychosis and suicidal ideation;
- CS-associated ADR is probably because of diminished central nervous system production of gamma-aminobutyric acid as a result of inhibition of glutamic decarboxylase;
- Treating physicians of all MDR-TB cases with ADR´s on CNS should have a very high degree of suspicion on CS.

Competing interests

The authors declare no competing interests.

Authors' contributions

All the authors have read and contributed equally to the manuscript.

References

1. Yadav S, Rawal G. Tubercular nodular episcleritis: a case report. J Clin Diagn Res. 2015;9(8):ND01-ND02. **PubMed** | **Google Scholar**

2. Yadav S, Rawal G. The novel concept of creating awareness about tuberculosis at the metro stations. Pan Afr Med J. 2016;23:228. **PubMed** | **Google Scholar**

3. Yadav S, Rawal G. Primary extrapulmonary multidrug-resistant tuberculosis of the sternum without HIV infection. J Clin Diagn Res. 2016;10(1):RD01-RD03. **PubMed** | **Google Scholar**

4. Yadav S. A new concept in tuberculosis awareness in the low-income countries. Edorium J Tuberc. 2015;1:1-4. **Google Scholar**

5. Vasisht AK, Yadav S. Role of a counselor in the management of multidrug-resistant TB. Indian Journal of Immunology and Respiratory Medicine. 2016;1(1):23-24. **Google Scholar**

6. Tandon VR, Rani N, Roshi, Gupta R, Arora M, Khajuria V *et al*. Cycloserine induced psychosis with hepatic dysfunction. Indian J Pharmacol. 2015;47(2):230-231. **PubMed** | **Google Scholar**

7. Sharma B, Handa R, Nagpal K, Prakash S, Gupta PK, Agrawal R. Cycloserine-induced psychosis in a young female with drug-resistant tuberculosis. Gen Hosp Psychiatry. 2014;36(4):451.e3-4. **PubMed** | **Google Scholar**

8. Bakhla AK, Gore PS, Srivastava SL. Cycloserine induced mania. Ind Psychiatry J. 2013;22(1):69-70. **PubMed** | **Google Scholar**

9. Fujita J, Sunada K, Hayashi H, Hayashihara K, Saito T. A case of multi-drug resistant tuberculosis showing psychiatric adverse effect by cycloserine. Kekkaku. 2008;83(1):21-25. **PubMed** | **Google Scholar**

10. 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):1257-1266. **PubMed** | **Google Scholar**

11. Behera C, Krishna K, Singh HR. Antitubercular drug-induced violent suicide of a hospitalised patient. BMJ Case Rep 2014. 2014 bcr2013201469. **PubMed** | **Google Scholar**

12. Lewis WC, Calden G, Thurston JR, Gilson WE. Psychiatric and neurological reactions to Cycloserine in the treatment of Tuberculosis. Chest. 1957;32(2):172-182. **PubMed** | **Google Scholar**

13. Johnson AW. Drug-induced psychiatric disorders. Drugs. 1981;22(1):57-69. **Google Scholar**

14. Yadav S, Rawal G. Role of integrating community health workers in achieving healthcare information for all. Int J Sci Res Rev. 2015;4(1):106-110.

15. Yadav S, Rawal G. Counterfeit drugs: Problem of developing and developed countries. Int J Pharmceut Chem Anal. 2015;2(1):46-50. **Google Scholar**

16. Yadav S, Rawal G. Primary extrapulmonary extensively drug resistant tuberculosis of the hip in an immunocompetent female: a case report. J Clin Diagn Res. 2017;11(1):LD01-LD03. **PubMed** | **Google Scholar**