Case Report

Cycloserine-induced psychosis in a young female with drug-resistant tuberculosis

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A B S T R A C T

Objective: To report a case of cycloserine-induced acute psychosis in a young female while on second line antitubercular treatment (ATT) for tubercular meningitis.

Method: Case report.

Results: A 20-year-old female, known case of tubercular meningitis on ATT since 8 months, presented with a 10-days history of headache, vomiting, and photophobia. A provisional diagnosis of drug-resistant tuberculosis was made, and second-line ATT including cycloserine (750 mg/day) and levofloxacin (750 mg/day) was added. Three days after the start of cycloserine and levofloxacin, the patient developed psychosis with delusions and hallucinations. Since the patient was on several drugs with potential to cause psychotic reaction, we considered a provisional diagnosis of drug-induced acute psychosis. Two days following cycloserine withdrawal, the patient improved significantly, and on the third day, she was absolutely normal with disappearance of psychotic symptoms.

Conclusion: Our case highlights the importance of awareness regarding psychiatric adverse events of antitubercular agents and the reversible nature of the adverse events on drug withdrawal. We also suggest that caution should be exercised while administering cycloserine in MDR-TB patients because of a higher risk of psychiatric adverse events.

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1. Introduction

Several antitubercular drugs are known to have neuropsychiatric adverse drug reactions; common among the frequently used agents are isoniazid, ethambutol, ethionamide and fluoroquinolones and others in this list [1–3]. We herein report a case of cycloserine-induced acute psychosis in a young female while on second-line antitubercular treatment (ATT) for tubercular meningitis.

2. Case report

A 20-year-old female who was nonalcoholic and with a known case of tubercular meningitis on ATT since 8 months presented with 10-day history of headache, vomiting and photophobia. The patient was on maintenance phase of ATT with isoniazid (300 mg/day) and rifampicin (450 mg/day). General physical examination, respiratory system, cardiovascular system and gastrointestinal system examinations were found to be normal. Neurological examination revealed normal motor and sensory functions; however, meningeal signs of irritation (neck rigidity and Kerning's sign) were present. Laboratory investigations showed increased erythrocyte sedimentation rate and reactive cerebrospinal fluid (CSF) with increased proteins (140 mg%) and cells (80 cells with 90% lymphocytes). CSF examination for polymerase chain reaction for tuberculosis was positive, whereas CSF India ink for Cryptococcus and fungal culture were negative. Serum cryptococcal antigen titer was also negative. Thus, a provisional diagnosis of drug-resistant tuberculosis was made, and second-line ATT including cycloserine (750 mg/day) and levofloxacin (750 mg/day) was added as she had already received injectable amikacin for 2 months during intensive phase. The patient's CSF was sent for culture and sensitivity for all first-line and second-line antitubercular drugs, results of which were expected after 3 to 4 weeks.

Three days after the start of cycloserine and levofloxacin, the patient's attendant complained that the patient had become very irritable and verbally abusive toward family members. She was notably found talking excessively and irrelevantly, talking to herself and was scared and felt that her brother was conspiring against her. She also believed that her friends and family members would make fun of her illness. A psychiatric consultation was obtained for her inappropriate psychiatric behavior, and a clinical diagnosis of acute psychosis with delusions and hallucinations was made and antipsychotic therapy with quetiapine (25 mg/day) was started. She was further evaluated for any possible cause. Her personal and family history was negative for any psychiatric illness. Magnetic resonance imaging (MRI) brain was obtained to rule out hydrocephalus or any vascular infarct. Patient's metabolic profile was found to be normal. Since the patient was on several drugs with potential to cause psychotic reaction, we considered a provisional diagnosis of drug-induced...
acute psychosis. We decided to eliminate one drug at a time. Since
cycloserine and levofloxacin were the most recent drugs to be added prior
to the episode, we first stopped cycloserine and the patient was kept
under observation. Two days following cycloserine withdrawal the
patient improved significantly, and on the third day, she was absolutely
normal with disappearance of psychotic symptoms. Quetiapine was
stopped on the same day. There was no recurrence of psychiatric
symptoms, and the patient was discharged 5 days following withdrawal
of cycloserine. On follow-up (10 days after discharge), the patient was
free of psychotic symptoms.

3. Discussion

Psychiatric comorbidities associated with tuberculosis and neuro-
sychiatric adverse effects of antitubercular drugs are additional
challenges to be taken care of while managing tuberculosis, as these
can affect compliance and therapy outcome [4,5].

Our patient had no personal or family history of psychiatric
 disorders, but was on several potential antitubercular drugs known to
cause psychotic reactions. Among antitubercular drugs, isoniazid is
most commonly associated with psychiatric adverse reactions, and
rarely, ethambutol can also be a causative agent [1,6]. Our patient was
on both isoniazid and ethambutol over months without any
psychiatric events noted prior to the current presentation. She
recovered while therapy with these drugs was maintained. Therefore,
isoniazid and ethambutol could be ruled out as culprits in our patient.
Recently, psychotic adverse reactions of fluoroquinolones including
levofloxacin are also being encountered [2]. Since psychotic features
in our patient recovered completely on cycloserine withdrawal, and
she was continued on levofloxacin without any recurrence of
symptoms, levofloxacin appears unlikely to be a cause in our case.
Considering the onset of psychotic reaction within 3 days of start of
cycloserine and complete remission of symptoms within 3 days of
withdrawal, cycloserine was the most likely offending drug in our
patient. Based on the Naranjo adverse drug reaction probability scale,
the event psychosis was assessed as possibly related to cycloserine.

Cycloserine was first introduced in 1954 as a broad-spectrum
antibiotic, but soon after its introduction, several serious psychiatric
and neurological adverse drug reactions were observed. With
the availability of drugs with higher efficacy and better safety profile,
the use of cycloserine became restricted as a second-line antitubercular
drug for multidrug-resistant tuberculosis (MDR-TB) [7].

Globally, 3.7% of new cases and 20% of previously treated cases
have been observed as MDR-TB cases wherein China, India and the
Russian Federation account for greater than 50% of the global burden
[8]. With MDR-TB being rampant, especially in resource-scarce
country like India, use of second-line ATT cycloserine has become
commonplace and has led to the resurgence of the side effects,
especially psychiatric reactions. Thus, awareness among clinician
regarding adverse events of the second-line drugs has become crucial.

Among second-line antitubercular drugs, cycloserine has the
highest frequency of neuropsychiatric adverse events [9]. Vallade,
Hugoneng and Jude had put forward few predisposing factors for
neuropsychiatric adverse events of cycloserine. These were emotion-
ally unstable personality, female gender, history of alcoholism and
higher dose (>1 g/day) of cycloserine. The incidence of psychiatric
adverse effect is twice high in females as compared with men [7,10].

4. Conclusion

Our case highlights the importance of awareness regarding psy-
chiatric adverse events of antitubercular agents and reversible nature
of the adverse events on drug withdrawal. In this era of drug-resistant
tuberculosis, it is important for neurologists and psychiatrists to be
aware of psychiatric manifestations of second-line antitubercular
drugs so that early diagnosis and treatment of this reversible
condition are undertaken and patient is not subjected to inadvertent
investigations. We also suggest that caution should be exercised
while administering cycloserine because of higher risk of psychiatric
adverse events.

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