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Case Report

ADR assessment of isoniazid induced psychosis: Case report and review of literature

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ABSTRACT

Tuberculosis ranks among the top 10 causes of death globally and stands as the primary cause attributed to a single infectious agent. Among all antitubercular drugs, Isoniazid is most important role in the management of pulmonary tuberculosis. Various neuropsychiatric adverse effects have been documented in association with the use of isoniazid, both in therapeutic and overdose scenarios. This case report describes a 68-year-old male with multiple health issues, including disseminated tuberculosis, developed drug-induced psychosis, likely due to isoniazid in his anti-tubercular therapy. This case underscores the challenges of psychiatric adverse effects in tuberculosis treatment and emphasizes the importance of prompt recognition and intervention.

1. Introduction

Psychosis is a serious mental illness that causes individuals to perceive the world differently. According to the National Alliance on Mental Illness, a psychotic episode occurs when a person loses contact with reality. Any episode linked to drug addiction, sometimes referred to as substance-induced psychotic disease, is termed drug-induced psychosis. Isonicotinic acid hydrazide, often known as isoniazid (INH), was discovered in 1912 and first used to treat tuberculosis by Robitzek over 50 years later, in 1952.[1] Isoniazid is the initial medicine in the DOTS regimen and is frequently used. Hepatitis, peripheral neurotoxicity, lupus-like syndrome, and adverse effects on the central nervous system, such as dysarthria, convulsions, agitation, and even psychosis, are some of the negative effects.[2,3] The most frequent side effects of isoniazid include hepatitis, rash, and peripheral neuropathy. Occasionally, reports of psychosis, convulsions, or even demise have been made. INH may lead to psychosis by inhibiting the monoamine oxidase enzyme and reducing N-Methyl D-Aspartate receptors due to the oxidative stress it causes.[3] Additionally, INH interacts with pyridoxine metabolism in tissues, creating a pyridoxal-INH complex, resulting in pyridoxine shortage and lower levels of inhibitory neurotransmitters. There have been reports of INH-induced psychosis as an adverse drug reaction in the literature[4,5]

2. Case Study

A 68-year-old male, weighing 64 kg was admitted in the tertiary care hospital with chief complaints of decreased appetite and weight loss in the last 6 months (15 kg), cough with minimal expectoration, evening rise of temperature.

Patient was diagnosed disseminated Kochs- miliary tuberculosis lung, left cerebellar granuloma, lesions in 11^{th} and 12^{th} Thoracic vertebrae, chronic liver disease COPD, BPH. There was no significant family history and past history of similar illness.

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Patient was admitted in pulmonary isolation ward, and was started on first line anti-tubercular therapy Rifampicin 600 mg OD, Isoniazid 300 mg OD, Ethambutol 800 mg OD, Pyrazinamide 1000 mg OD, will increase if patient tolerating, B6 40 mg OD, Prednisolone 60 mg od, Rabeprazole 20 mg BD.

The first 3 days of treatment with this four-drug regimen was uneventful. On the fifth day, the patient suddenly became restless, with abnormal behavior, altered sensory centers, indifferent speech, agitated behavior, stubbornness, inappropriate urination, sleep deprivation, and decreased response to commands. In view of these sudden altered behavioural patterns, psychiatry consultation was done. An initial diagnosis of drug induced psychosis was made after a psychiatric consultation, possibly of isoniazid induced psychosis.

Psychiatric chemotherapy was advised with Serenace 2.5 mg slow intravenous injection and 1 mg Lorazepam Intramuscularly as a single dose. Oral preparation of 5mg Olanzepam twice daily for 5 days, on 8^{th} day, isoniazid was excluded from the treatment and pyridoxine 80mg once daily per orally was added to therapy. Patient condition improved in terms of sensorium and he became oriented, cooperative with proper food intake, adequate sleep, social interactions and good personal hygiene. As per psychiatric assessment he was discharged with the advice to continue modified ATT with pyridoxine and frequent follow ups.

3. ADR Analysis

After examining the antitubercular medications ADR profiles, it was determined that the medicine most likely to cause psychosis was isoniazid. As clinicians, we did additional assessments to establish a link between the likely medicine and the produced adverse response, using Naranjo's scale,[6] as shown in the below Table 1.

Table 1: Causality assessment of suspected ADRs.

ADRs	Causality (Naranjo's Scale)
Isoniazid induced Psychosis	Naranjo's Scale

We made an, further assessment on the severity, predictability and preventability through Modified Hartwig and Siegel severity scale, Schumock and Thornton Preventability Scale which were represented in the below Table 2.

Table 2: Severity, predictability and preventability of suspected ADR

Drug	Severi Everity	Predictability	Preventability
Isoniazid	Moderate	Predictable (Type A)	Probably preventable

4. ADR Management

Usually, management of ADRs includes withdrawal/suspension, dose reduction of suspected/probable drugs and administration of supportive therapy by addition of an antipsychotic. Here in this issue, to treat ATT (Isoniazid) Induced psychosis the drug was withdrawn and modified ATT therapy was given.

5. Discussion

Tuberculosis is still a major public health issue in India. Although the disease's incidence and prevalence have dropped in recent decades, it still accounts for the greatest number of DALYs lost among communicable diseases. HIV infection, as well as socioeconomic issues such as poverty, homelessness, and drug misuse, may all contribute to a rise in the number of TB cases.[7] As per the Global TB Report for the year 2021, India recorded an estimated incidence rate of 188 per 100,000 population and a prevalence rate of 316 per lakh population for all forms of tuberculosis.[8] Isoniazid (5 mg/kg once daily), Rifampicin (10 mg/kg once daily), Ethambutol (15–25 mg/kg once daily), and Pyrazinamide (20–30 mg/kg once daily) are the first-line treatments for tuberculosis.[2] The management of tuberculosis is severely hindered by psychiatric ADR, which also significantly reduces an ATT patient's quality of life. Mandel et al. reported the first description of psychotic symptoms caused by INH in 1956. Isoniazid inhibits the activity of pyridoxal-5-phosphate in the brain, which is produced by the body from pyridoxine, this decrease in gamma-aminobutyric acid and other synaptic transmitters has negative effects on the nervous system.[1] In substance-induced psychotic disorders, symptoms may remain for weeks or more after the hazardous substance has been removed. There may occasionally be signs of depression, heightened anxiety, emotional instability, depersonalization, and repeated amnesia. Predisposing parameters for isoniazid-induced psychosis include a prior history of psychiatric or neurological illness, alcoholism, diabetes mellitus, malnutrition, uraemia, hepatic insufficiency, and a dose of Isoniazid greater than 5 mg/kg.[9–11] It is unclear what causes Isoniazid (INH) to cause neuronal damage. There are two theories put up by Pallone et al. regarding the mechanism of isoniazid-related psychosis.[12] The first is that isoniazid functions as a monoamine oxidase inhibitor, delaying the breakdown of serotonin and catecholamines, increasing their concentrations in the CNS. Another mechanism widely established is that INH causes both acute psychosis and peripheral neuropathy due to pyridoxine deficiency induced by isoniazid.

INH metabolites prevent pyridoxine from being activated to pyridoxal 5-phosphate. which is an important coenzyme in the metabolism of amino acids, This result in a decrease in the metabolism of amino acids to dopamine,

norepinephrine, and serotonin. After administering a loading dose of tryptophan, patients with pyridoxine insufficiency excrete various tryptophan metabolites in their urine. This test can also be utilized to identify pyridoxine deficiency.[13]

Another factor for the sudden onset of psychosis could be the drug's pharmacokinetic characteristics.[12] INH is rapidly absorbed from the gastrointestinal system, reaching peak levels within 1 to 2 hours of intake of a therapeutic dose.[14] About 40% of Indians have been shown to be slow acetylators, which slows metabolism and increases drug accumulation and adverse outcomes.[12]The most common treatment for INH-induced psychosis is to withdraw the drug, treat the psychosis, and then gradually reintroduce INH at a lower dosage after the psychosis is resolved.[15–17] In a case mirroring drug-induced psychosis, a 31-year-old male developed symptoms like incoherent speech and paranoid ideation four weeks into Isoniazid (INH)-based antitubercular therapy. Despite discontinuing all drugs, symptoms persisted, leading to an INH-induced psychosis diagnosis. Olanzapine provided relief, and while other antitubercular drugs were reintroduced without issues, INH was substituted with levofloxacin. Within 15 days of Olanzapine, the patient became asymptomatic, highlighting the necessity for timely intervention in drug-induced psychiatric complications during tuberculosis treatment.[7] According to study findings, in cases when psychiatric symptoms are not severe, INH can be used in conjunction with new antipsychotics such as risperidone and olanzapine to treat the psychiatric presentation.[18] The prevalence of tuberculosis is higher in developing nations like India. The drug toxicity profiles of anti-tubercular medications like INH should therefore be known to clinicians. It is advised that the patient must be followed up after 15 days to assess whether or not his condition has improved as a result of receiving supportive therapy.

6. Conclusion

DOTS therapy has undoubtedly demonstrated its effectiveness in achieving high cure rates; however, due to the elevated drug dosages, issues related to tolerance and complications remain a concern. To prevent neurological complications, pyridoxine tablets should be added to the ATT regimen. The sudden onset of psychotic symptoms in an isoniazid-taking patient should raise suspicions about this mental side effect and urgent action, such as stopping the medication and/or initiating an antipsychotic, should be considered. Thus, clinicians should be aware of the drug toxicity profiles of anti-tubercular drugs like INH and monitor the vitals and systems at risk at regular intervals during therapy to minimize drug-induced reactions.

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9. Abbreviation

1. TB: Tuberculosis
2. INH: Isoniazid
3. ATT: Anti tubercular therapy
4. DOTS: Directly observed therapy
5. DALYs: Disability adjusted life year
6. COPD: Chronic obstructive pulmonary disease
7. BPH: Benign prostate hyperplasia

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None.

11. Conflicts of Interest

All Authors declares that there are no conflicts of interest.

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