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Isoniazid-Induced Psychosis in a Patient with Pulmonary Tuberculosis: A Case Report

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Abstract
Isoniazid is one of the most important drugs in the management of pulmonary tuberculosis; of all the antituberculous drugs, it is one of the most commonly implicated drugs in drug-induced psychosis. We report a case of isoniazid-induced psychosis in a 31-year-old patient with pulmonary tuberculosis.

Introduction

Isoniazid (isonicotinic acid hydrazide), also called INH, is a first-line drug in the treatment of tuberculosis (TB). INH has been in use for the treatment of TB for many decades. It still remains one of the most effective and specific drugs used in TB [1].

The South-East Asian region bears the maximum burden of TB with a catastrophic economic and social impact. According to the Global TB Report 2021, the estimated incidence and prevalence of all forms of TB in India were 188 per 100,000 population and 316 per lakh population, respectively [2].

India has the highest prevalence of TB in the world [3]. Psychosis is a mental disorder characterized by delusions, hallucinations, and confused thoughts and behavior which causes people to perceive or interpret things differently [4]. Substance-induced psychosis, also

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known as drug-induced psychotic disorder, is any psychotic episode that is related to the consumption of an offending medicine [5].

India has the highest incidence and prevalence of TB around the globe, making it a major health problem, and INH is one of the fundamental 1st line drugs used in its treatment. There remains a scarcity of the literature on the incidence and prevalence of INH-induced psychosis, and this case report could help fortify the existing knowledge of the same and could help clinicians at large in guiding through a differential of acute psychosis in patients on antituberculous therapy (ATT), especially in predisposed individuals. Hence, we report a case of suspected INH-induced psychosis.

Case Report

A 31-year-old male educated up to 10th standard, shopkeeper by profession, belonging to middle socio-economic strata in an urban area with no prior psychiatric history was brought by his wife to the psychiatry outpatient department with the complaints of incoherent speech, garbled sentences, paranoid ideation regarding his family (plotting against him and conspiring to steal his belongings), listening to voices (auditory hallucinations), and shouting at people who were not around since the last 2 days. These symptoms were associated with intermittent insomnia and a desire to stay in isolation and darkness.

The symptoms started about 4 weeks after he was put on INH 300 mg/day, rifampicin 600 mg/day, ethambutol 800 mg/day, and pyrazinamide 1,500 mg/day for pulmonary TB and pyridoxine (vitamin B6) 20 mg/day for prophylaxis against neuropathy by the prescribing physician. There was no history of recent ingestion of any psychoactive substances. His brother had a distant history of social anxiety disorder/social phobia, and his sister had a positive past history of bulimia nervosa in her teenage years that resolved after 4 months of treatment.

The physical examination was unremarkable, and the vital signs were stable, and testing including a complete blood count, chest X-ray, and urine toxicology screening were all within the normal ranges. A thyroid function test initially showed a marginally low thyroid-stimulating hormone with normal triiodothyronine and thyroxine. A computed tomography scan of the head showed no abnormality. Due to the absence of any other eminent cause of this behavior change, an initial diagnosis of drug-induced psychosis due to INH was contemplated.

Thereafter, all the antitubercular therapy was stopped by the prescribing physician. Although he responded minimally after INH was stopped, the auditory hallucinations, shouting, and the paranoid ideation still persisted. Subsequently, the patient was put on tablet olanzapine 10 mg/day and tablet lorazepam 2 mg/day by the treating psychiatrist. Rifampicin, pyrazinamide, and ethambutol were successively reintroduced, to monitor a possible relapse of symptoms. INH was not reintroduced as it was the most likely offending drug taken into consideration for the symptoms and was subsequently replaced with tablet levofloxacin 750 mg/day by the treating physician to complete the antitubercular treatment regimen as per the standard treatment guidelines. Eventually, the patient became asymptomatic after taking olanzapine for a period of 15 days.

The patient did not require olanzapine and lorazepam 7 weeks after his visit to the treating physician and also agreed for follow-ups. He remained asymptomatic at the subsequent follow-up visits to the hospital.

The Brief Psychiatric Rating Scale (BPRS) is a commonly employed scale that is used to establish the possible presence and severity of various psychiatric disorders [6]. The BPRS score was evaluated to be 47 in this patient as per the treating psychiatrist on the 5th day, thereby determining the severity as moderate.

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The causality assessment of the adverse drug reaction came out to be possible for this case using the Naranjo Causality Assessment Scale [7]. The case was reported to the adverse drug reaction monitoring center under the Pharmacovigilance Programme of India (PvPI).

Discussion

TB remains a major health problem in India. Although, the incidence and prevalence of the disease have witnessed a steady decline when compared with the previous decades, it still accounts for the maximum disability adjusted life years lost among the various communicable diseases. Various factors including HIV infection, poverty, undernutrition, homelessness, and drug abuse may lead to an increase in the prevalence of TB [8].

In this case, the patient was diagnosed as a case of primary pulmonary TB and initially started on an intensive 2 months regimen consisting of standard four first-line drugs INH, rifampicin, pyrazinamide, and ethambutol. The BPRS is one of the oldest rating scales, used by clinicians and researchers to evaluate several psychiatric symptoms such as depression, anxiety, and psychosis. The scale was first published in 1962 and was later expanded to 18 items and subsequently to a 24-item scale. The 24 items are graded on a scale from 1 (not present) to 7 (extremely severe), and 0 is marked if any item is not assessed. The total of the scores ranges between 24 and 168, with higher scores indicating more severe psychopathology [9]. The severity of the BPRS scale is graded as mild (31–40 total score), moderate (41–52 total score), and severe (above 52 total score) [10].

The temporal association of administration of antitubercular therapy and the onset of psychotic symptoms in the absence of previous psychiatric history strongly suggested a diagnosis of drug-induced psychosis. Of all the antitubercular drugs, INH is the most implicated in cases of acute psychosis secondary to therapy. Hence, INH was first considered in our case to be responsible for the psychotic episode.

Besides psychosis, INH has been implicated in a number of other neuropsychiatric conditions including paranoia, obsessive-compulsive disorder, depression, and mania [11]. Several non-neuropsychiatric conditions including peripheral neuropathy, sleep disturbances, headache, and blurring of vision have been associated with the use of INH [12].

In this case, the patient developed psychotic symptoms 4 weeks after initiation of the antitubercular therapy. The symptoms remitted 15 days after ATT discontinuation and commencement of olanzapine 10 mg/day and lorazepam 2 mg/day. Subsequently, both the drugs were withdrawn, and there was no recurrence throughout the course of his antitubercular treatment.

The presentation of the patient and remission of the symptoms were similar to the case of a 21-year-old female with an unremarkable psychiatric history, who experienced acute-onset paranoid delusions, agitation, and insomnia within 4 days of initiating INH 300 mg as a part of an intensive phase of the ATT regimen; the symptoms resolved completely within 21 days of initiating olanzapine [12].

Similarly, another patient of INH-induced psychosis with previously unremarkable psychiatric history presented with acute psychosis within 12 days of ATT initiation which resolved completely within 2 days of ATT discontinuation [13]. The self-resolution of the symptoms immediately after cessation of therapy and the absence of any personal or family history of psychosis in this patient were seen in contrast to our case.

The drug-induced psychotic symptoms usually range from a few days to 2 months after the treatment onset with INH [14]. Although the exact cause remains obscure, there are a few suggested mechanisms for INH-associated psychosis. The postulated mechanisms implicate

INH acting as a monoamine-oxidase inhibitor, an over- or underproduction of the monoamine neurotransmitters serotonin, dopamine, and norepinephrine.

One of the mechanisms involves INH acting as a nonselective monoamine-oxidase inhibitor, thus preventing the degradation of monoamines, i.e., epinephrine, norepinephrine, serotonin, and also dopamine, ultimately leading to a raised concentration of these neurotransmitters; primarily, dopamine and serotonin at the synapse act on the dopaminergic receptors, leading to psychotic symptoms [15].

Another mechanism suggests that the use of INH leads to a pyridoxine deficiency, ultimately leading to a reduction in the concentration of the neurotransmitters. INH combines with pyridoxine 5'-phosphate and pyridoxal 5'-phosphate (a metabolite of vitamin B6) to form a complex that inhibits the action of pyridoxal kinase. The action of pyridoxal kinase is to convert pyridoxal to pyridoxal phosphate, which is an important coenzyme in the metabolism of amino acids, including tyrosine and tryptophan (precursors of catecholamines). Pyridoxal 5□-phosphate is an active form of vitamin-B6, which acts as a cofactor in the synthesis of gamma amino butyric acid (GABA); this leads to depletion in the levels of GABA. Decrease in the levels of GABA has been implicated in many disorders including psychosis [16].

Patients with pyridoxine deficiency excrete a number of metabolites of tryptophan in the urine (e.g., xanthurenic acid), after a loading dose of tryptophan is given. This test could also be used to assess pyridoxine deficiency status in addition to obtaining a blood concentration. However, pyridoxine deficiency is less likely in our patient as she was taking a pyridoxine supplement. Although, the exact mechanism remains to be elucidated, the clinicians should be wary of the possibility of INH-induced psychosis [16]. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530779).

Statement of Ethics

Ethical approval is not required from the Ethical Committee as this case report was in accordance with local guidelines. Written and informed consent was obtained from the patient for publication of the details of their medical case in the manuscript. There are no images accompanying the case.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Dr. Shreshth Khanna has made substantial contributions to the conception or design, acquisition of literature material, and revising it critically for important intellectual content. Dr. Suchita Pant has made significant contributions to acquisition of literature material

relevant to the case report. Dr. Harsh Khanna has made significant contributions to revising it critically for important intellectual content.

Data Availability Statement

All data that support the findings of this study are included in this article. Further inquiries can be directed to the corresponding author.

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