**ADR ASSESSMENT OF ISONIAZID INDUCED PSYCHOSIS: CASE REPORT AND REVIEW OF LITERATURE**

**ABSTRACT**

**INTRODUCTION**

Tuberculosis is one among the major public health issues in developing and underdeveloped nations. Isoniazid, rifampicin, ethambutol, and pyrazinamide are the medications used as first-line treatment for TB. Isoniazid is being the first line anti - TB agent for the treatment of tuberculosis, we are documenting a case of Isoniazid induced psychotic illness as an adverse drug reaction.

**CASE REPORT**

A 68-year-old male complaints of loss of weight, appetite, chronic of with expectoration and evening raise of temperature of six-month duration, was admitted and diagnosed pulmonary tuberculosis by clinical evaluation and microbiological confirmation by sputum examination. Anti-tubercular therapy was started with Isoniazid, Ethambutol, Pyrazinamide, and Rifampicin. On the fifth day of therapy abnormal behaviour altered sensorium noted, psychiatric revealed the possibility of drug induced psychosis.

**CONCLUSION**

**Since drug induced psychosis of Isoniazid is a known adverse drug reaction, early diagnosis, chemotherapeutic management along with** proper patient counselling & patient’s education is pivotal for optimum clinical outcome.

KEY WORDS

Isoniazid, drug induced psychosis, tuberculosis, adverse drug reaction

**INTRODUCTION**

Psychosis is a serious mental illness that makes people experience or interpret the world in ways that are different from others around them. According to the National Alliance on Mental Illness, a psychotic episode occurs when a person loses contact with reality. Any psychotic episode that is linked to drug addiction, sometimes referred to as substance-induced psychotic disease, is referred to as drug-induced psychosis. Isonicotinic acid hydrazide, often known as isoniazid (INH), was initially discovered in 1912 and was first used to treat tuberculosis by Robitzek more than 50 years later, in 1952(1). The first medicine in the DOTS regimen and one that is frequently used is isoniazid. Hepatitis, peripheral neurotoxicity, lupus-like syndrome, and adverse effects on the central nervous system, such as dysarthria, convulsions, agitation, and even psychosis, are only a few of the negative effects (2) The most frequent side effects of isoniazid are hepatitis, rash, and peripheral neuropathy. Occasionally have reports of psychosis, convulsions, or even demise been made. INH may lead to by inhibiting the monoamine oxidase enzyme and decreasing the N-Methyl D-Aspartate receptors due to the oxidative stress INH causes, it may lead to psychosis.3In addition, INH interacts with pyridoxine metabolism in tissues to create a pyridoxal-INH complex, which results in pyridoxine shortage and lower levels of inhibitory neurotransmitters. There were INH-induced psychosis as an adverse drug reaction reported in literature.4,5

**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 11th and 12th Thoracic vertebrae, chronic liver disease COPD, BPH. There was no significant family history and past history of similar illness.

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 8th 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.

**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 (8), as shown in the below table No 1.

**Table no: 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 No.02.

**Table no: 2**: Severity, Predictability and Preventability of suspected ADR

| DRUG | SEVERITY | PREDICTABILITY | PREVENTABILITY |
| --- | --- | --- | --- |
| Isoniazid | Moderate | Predictable (Type A) | Probably preventable |

**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.

**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.(20) 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. (10-13) 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. (14) 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. (9)

Another factor for the sudden onset of psychosis could be the drug's pharmacokinetic characteristics. (14) INH is rapidly absorbed from the gastrointestinal system, reaching peak levels within 1 to 2 hours of intake of a therapeutic dose. (15) About 40% of Indians have been shown to be slow acetylators, which slows metabolism and increases drug accumulation and adverse outcomes. (14) 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. (16-18) 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. (19) 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.

**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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**Author’s contribution**

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**Conflicts of Interest**

All Authors declares that there are no conflicts of interest.

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**ABBREVIATIONS**

TB -Tuberculosis

INH - Isoniazid

ATT -Anti tubercular therapy

DOTS -Directly observed therapy

DALYs -Disability adjusted life year

COPD -Chronic obstructive pulmonary disease

BPH -Benign prostate hyperplasia

**REFERENCE**

1. Sharad Chand , Ramesh Bhandari , H.N. Girish , Degam Sukeerthi. Isoniazid Induced Psychosis. Journal of Global Pharma Technology. 2019 ;11( 5):11-14.
2. Rohit Bangwa, Jagdish Rawat, Yogesh Joshi. Isoniazid Induced Psychosis: A Case Report. Journal of Pharmaceutical Research and Clinical Practice. 2020 ;3 ( 1);23-25.
3. Taranjeet Kaur, Kanwalpreet Kaur and Preeti Malhotra. Isoniazid Induced Psychosis: A Case Report. Journal of Nepal Paediatric Society. 2019;39(3):189-92.
4. Drug Bank. Isoniazid; 2013. Available: http://www.drugbank.ca/drugs/D B00951 (Accessed 4 April 2013).
5. Arya S, Sukhija G, Singh H. Acute psychosis after recent isoniazid initiation. Journal of clinical and diagnostic research: JCDR. 2015;9(6): 45-55.
6. Masood I, Bhat S, Beigh A, Gupta V. Isoniazid-induced psychosis in a patient on DOTS therapy. Ann Trop Med Public Health. 2011;4(2):126-7.
7. (Adverse Drug Reaction Probability Scale (Naranjo) in Drug Induced Liver Injury - LiverTox - NCBI Bookshelf, 2019)Marcus R, Coulston AM. Water-soluble vitamins: The vitamin B complex and ascorbic acid. In: Goodman AG, Ruddon RW, Molinoff PB, Limbird LE, Hardman JG, editors. Goodman and Gilman’s the pharmacological basis of therapeutics. 9th Ed. New York: McGraw Hill, 1995:1555-71.
8. H. S. Duggal and S. H. Nizamie, “Novel antipsychotic drugs and INH-related psychosis,” Australian & New Zealand Journal of Psychiatry, vol. 34, no. 2, pp. 343-344, 2000.
9. S. Arya, G. Sukhija, and H. Singh, “Acute psychosis after recent isoniazid initiation,” Journal of Clinical and Diagnostic Research, vol. 9, no. 6, pp. VD01–VD02, 2015.
10. K. A. Pallone, M. P. Goldman, M. A. Fuller, L. Gonzalez, and C. Fiset, “Isoniazid-associated psychosis: Case report and review of the literature,” Annals of Pharmacotherapy, vol. 27, no. 2, pp. 167–170, 1993.
11. J. B. Silva Jr., “Tuberculose: Guia de Vigilância Epidemiológica,” Jornal Brasileiro de Pneumologia, vol. 30, no. 1, pp. S57–S86, 2004.
12. K. A. Pallone, M. P. Goldman, M. A. Fuller, L. Gonzalez, and C. Fiset, “Isoniazid-associated psychosis: Case report and review of the literature,” Annals of Pharmacotherapy, vol. 27, no. 2, pp. 167–170, 1993.
13. Arya S, Sukhija G, Singh H. Acute psychosis after recent isoniazid initiation. Journal of clinical and diagnostic research: JCDR. 2015 Jun;9(6):VD01.
14. Iannaccone R, Sue YJ, Avner JR. Suicidal psychosis secondary to isoniazid. Pediatric emergency care. 2002;18(1):25-7.
15. Binwal VK, Syed T, Ahir D. Isoniazid induced cerebellitis and psychosis in chronic kidney disease patient with tubercular pleural effusion. J IntegrNephrolAndrol. 2016;3(2):60-1.
16. Duncan H, Kerr D. Toxic psychosis due to isoniazid. British journal of diseases of the chest. 1962;56(3):131-8
17. Oninla SO, Oyedeji GA, Oninla OA, Gbadebo-Aina. Isoniazid induced psychosis in two children treated for tuberculosis: case reports and literature review. IJMPCR. 2016;6(4):1-6
18. . Isoniazid induced psychosis- a clinical dilemma. J Indian Acad Clin Med. 2002;3(3):306-7.
19. Millet JP, Moreno A, Fina L, del Baño L, Orcau A, de Olalla PG, Caylà JA. Factors that influence current tuberculosis epidemiology. Eur Spine J. 2013 Jun;22 Suppl 4(Suppl 4):539-48. doi: 10.1007/s00586-012-2334-8. Epub 2012 May 8. PMID: 22565801; PMCID: PMC3691414.