ISSN 2394 - 2053 (Print)
ISSN 2394 - 2061 (Online)
RNI: ASSENG/2016/70661
www.ojpas.com

CASE SERIES

Open Journal of Psychiatry & Allied Sciences

Isoniazid associated psychosis: case series from a tertiary care centre

Abstract

Isoniazid (INH) is a commonly used first line antitubercular drug. INH associated psychosis is a rare psychiatric manifestation. We report two cases of pulmonary tuberculosis, where the patients developed psychosis after being given a therapeutic dose of INH. In vulnerable patients, INH may cause change in concentration of neurotransmitters by inhibition of monoamine oxidase (MAO) and deficiency of pyridoxine. This might precipitate psychosis. Our observation also supports the hypothesis that INH associated psychotic disorders might have a pathophysiological substrate in common with some schizophrenia patients, who show remarkable response to low doses of atypical antipsychotic agents and pyridoxine supplementation.

Keywords: Antitubercular Agents. Antipsychotic Agents. Pyridoxine.

Hemendra Singh[1], Gayathri Devi HJ[2], Mamatha Chabaria[3], Kartik Shekar[4]

[1]Assistant Professor, Department of Psychiatry, M.S. Ramaiah Medical College, Bangalore, Karnataka, India, [2]Associate Professor, Department of Respiratory Medicine, M.S. Ramaiah Medical College, Bangalore, Karnataka, India, [3,4]Intern, Department of Psychiatry, M.S. Ramaiah Medical College, Bangalore, Karnataka, India

Correspondence: Dr. Gayathri Devi HJ, MBBS, DTCD, MD (Chest), FCCP, Professor & HOD, Respiratory Medicine, M.S. Ramaiah Medical College, Consultant Pulmonologist, M.S. Ramaiah Memorial Hospital, Bangalore-560054, Karnataka, India.
gayathrijoshy@gmail.com

Received: 21 March 2017
Revised: 1 June 2017
Accepted: 1 June 2017
Epub: 26 October 2017

INTRODUCTION

Isoniazid (INH) is a commonly used first line antitubercular drug because of its low cost and high potency. INH toxicity most often presents as peripheral neuropathy, hepatitis, and rash. Less often reported side effects include acute psychosis, convulsions, and even death. In patients with tubercular meningitis, the aetiology of psychotic symptoms become hard to determine, as they could be either because of the organic pathology or due to INH associated psychosis.[1] Hence, organic causes of psychosis always need to be ruled out before arriving at this diagnosis. We present two cases of INH associated psychiatric disturbances that we encountered at M.S. Ramaiah Teaching Hospital.

CASE 1

Miss A, an 18 years old female presented with catatonic symptoms such as mutism, staring look of eight hours duration. She had been hesitant to use the washroom due to fear and was under the delusion that she was already dead for three days before the onset of catatonia. Miss A had been diagnosed with pulmonary tuberculosis one week ago following hospitalisation for a febrile illness. She had been on first line antitubercular therapy (ATT) as per Directly Observed Treatment, Short course (DOTS) category 1 regimen (INH 600 mg, rifampicin 450 mg, pyrazinamide 1500 mg, and ethambutol 1200 mg in a thrice weekly schedule). The patient was admitted under a provisional diagnosis of acute INH associated psychosis with catatonia. Patient had no history of any substance abuse and neither had past or family history of psychiatric illness. Systemic examination revealed decreased air entry on right side of chest. Chest X-ray showed minimal pleural effusion on right side. Signs of meningeal irritation were absent.

A panel of other tests including complete blood count (CBC), liver function tests (LFTs), renal function tests (RFTs), Widal test, thyroid profile, serum vitamin B12, magnetic resonance imaging (MRI) brain (plain), lumbar puncture (LP) and cerebrospinal fluid (CSF) for cell count, India ink, acid fast bacilli (AFB), and Gram stain were found to be normal.

The patient was started on risperidone up to 4 mg per day and lorazepam 2 mg thrice a day. After four days of therapy, the patient's mental status appeared to be completely normal again. Patient was advised to continue ATT under DOTS along with the antipsychotic and pyridoxine supplements. She was symptom free on follow up after stopping the antipsychotic drug at the end of one month.

CASE 2

Mrs V, a 51 years old lady, was admitted to the Intensive Care Unit (ICU) for miliary tuberculosis and acute kidney injury. Patient was on first line ATT as per DOTS category 1 regimen. Patient developed altered behaviour within a week of starting ATT in the form of persecutory delusions, second and third person auditory hallucinations in clear consciousness. A provisional diagnosis of INH associated psychosis was made and patient was started on lorazepam 2 mg and risperidone up to 4 mg once daily. Patient had no past and family history of psychiatric illness. Physical examination was unremarkable except for bilateral crepitation and low baseline blood pressure (90/60 mm Hg). CBC, thyroid profile and urine routines were normal. LFTs/RFTs were deranged- total and direct bilirubin, alkaline phosphatase were elevated, albumin:globulin ratio was decreased, serum creatinine was elevated, and the patient also had hyperkalaemia and hyponatraemia. MRI brain was done to rule out any organic lesions and was normal. Ultrasonography of the abdomen and pelvis revealed bilateral grade two nephropathy and right sided pleural effusion. Correction of electrolyte imbalance was done on the day of admission.

In view of suspected drug associated hepatitis and psychosis, INH was stopped and patient was started on amikacin 500 mg, levofloxacin 500 mg, and ethambutol 400 mg (second line ATT). She was treated with risperidone and her psychotic symptoms gradually resolved. She was symptom free on follow up after one month, after stopping the antipsychotic medication.

DISCUSSION

Our cases developed psychosis within a week of initiation of treatment with ATT which is within the range of previously reported cases.[2] Psychosis due to INH is also reported in patients with family history of psychosis.[3] However, our both patients did not have any antecedent or family history of psychiatric illness, and had been exposed for a relatively short duration to INH. As both of our patients were also on other ATT medications, possible contributing role of other medications into development of psychotic symptoms could not be ascertained due to lack of explanation of biological mechanism. In our second case, psychotic symptoms were persistent even after treating underlying electrolyte disturbance which might also have contributed to behavioural problems. Raised hepatic and renal parameters could also be contributing factors other than INH. The causality assessments of the adverse drug reactions were performed by using the World Health Organization (WHO) and Naranjo's causality scales.[4,5] As per the WHO scale, the adverse drug reactions were found to be 'possible' in its causality. Naranjo's causality scale score for this reaction was found to be four for both cases, which implies that the adverse drug reaction was 'possible' due to the drug (Table 1). We have stopped INH in our second case as patient also had hepatic toxicity due to INH and in our first case INH was continued as patient was tolerating INH under coverage of antipsychotic drug.

Various mechanisms have been proposed regarding INH associated psychosis and rationale of using atypical antipsychotic drugs and pyridoxine for treatment. INH causes vitamin B6 deficiency by increasing its excretion.[6] Pyridoxal-5-phosphate is a cofactor of the enzyme glutamic acid decarboxylase that catalyses the conversion of glutamic acid to gamma-aminobutyric acid (GABA).[7] This results in depletion of GABA. This decrease in GABA also contributes in the aetiology of psychosis.[8] Role of an antibody to the enzyme glutamic acid decarboxylase (GAD) was reported as another possible cause of chronic psychotic disorders.[9] Clozapine helps in the treatment of psychosis by facilitating release of GABA.[10] Similar action of risperidone in treatment of INH related psychosis can be postulated. Supplemental doses of B6 help in psychosis via increased production of GABA. In our first case, psychotic symptoms resolved with risperidone (atypical antipsychotic drug) and pyridoxine supplementation, which is consistent with earlier report.[11] In our first case, catatonic symptoms reversed with lorazepam through increase GABAergic inhibition. Hence, this also supports the role of low GABA level in INH associated catatonia.

Change in level of other neurotransmitters could also be a possible explanation of INH associated psychosis. INH might act as a weak non-selective irreversible inhibitor of

Table 1: Naranjo's algorithm

Question	Yes	No	Do not know
Are there previous conclusion reports on this reaction?	**+1**	0	0
Did the ADR appear after the suspect drug was administered?	**+2**	−1	0
Did the ADR improve when the drug was discontinued or a specific antagonist was administered?	**+1**	0	0
Did the ADR reappear when drug was readministered?	+2	−1	**0**
Are there alternatives causes [other than the drug] that could solely have caused the reaction?	−1	+2	**0**
Did the reaction reappear when a placebo was given?	−1	+1	**0**
Was the drug detected in the blood [or other fluids] in a concentration known to be toxic?	+1	0	**0**
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	**0**
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	**0**
Was the adverse event confirmed by objective evidence?	+1	0	**0**
The total score calculated from this table defines the category as: definite (>9); probable (5 to 8); possible (1 to 4) and unlikely (<0)			

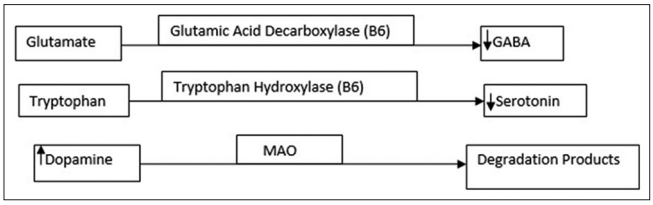

Figure 1: Possible mechanism of isoniazid associated psychosis. B6=vitamin B6, also called pyridoxine; GABA=gamma-aminobutyric acid; MAO=monoamine oxidase

monoamine oxidase (MAO) enzyme.[12] This inhibition prevents dopamine degradation and results in psychotic symptoms due to high level of dopamine. Hence, this supports the dopamine hypothesis of psychosis where increase level of dopamine by dopamine agonists (e.g. L-dopa, cocaine, and amphetamine) can induce psychosis.[13] Pyridoxal phosphate also serves as the coenzyme for hydroxytryptophan decarboxylase, which is required for the synthesis of serotonin from tryptophan. It was earlier hypothesised based on previous report that supplementation of pyridoxine might improve the drug associated psychosis by restoration of deficiency of cerebral serotonin and melatonin level.[14] Figure 1 illustrates the possible mechanism of INH associated psychosis.

Conclusion

Our observation supports the hypothesis that INH associated psychosis might have a pathophysiological substrate (increased dopamine level, and decreased serotonin and GABA levels) in common with some schizophrenia patients who show remarkable response to low doses of atypical antipsychotic agents. Supplementation of pyridoxine may potentiate response of atypical antipsychotic drugs in prevention of psychosis by increasing GABAergic inhibition of dopamine. Hence, supplement of pyridoxine along with atypical antipsychotic drug might be recommended in tuberculosis patients with psychosis who needs INH therapy for treatment.

REFERENCES

1. Masood I, Bhat S, Beigh A, Gupta V. Isoniazid-induced psychosis in a patient on DOTS therapy. Ann Trop Med Public Health. 2011;4:126-7.
2. Duncan H, Kerr D. Toxic psychosis due to isoniazid. Br J Dis Chest. 1962;56:131-8.
3. Goldman AL, Braman SS. Isoniazid: a review with emphasis on adverse effects. Chest. 1972;62:71-7.
4. The Uppsala Monitoring Centre. The use of the WHO–UMC system for standardised case causality assessment [Internet]. [cited 2017 Sep 3]. Avialbale from: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf
5. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45.
6. Biehl JP, Vilter RW. Effects of isoniazid on pyridoxine metabolism. J Am Med Assoc. 1954;156:1549-52.
7. DrugBank. Isoniazid. The Metabolomics Innovation Centre [Internet]. 2017 Sep 1 [cited 2017 Sep 3]. Available from: http://www.drugbank.ca/drugs/DB00951.
8. Roberts E. Prospects for research on schizophrenia. An hypotheses suggesting that there is a defect in the GABA system in schizophrenia. Neurosci Res Program Bull. 1972;10:468-82.
9. Yarlagadda A, Helvink B, Chou C, Clayton AH. Blood brain barrier: the role of GAD antibodies in psychiatry. Psychiatry (Edgmont). 2007;4(6):57-9.
10. Meltzer HY. The mechanism of action of novel antipsychotic drugs. Schizophr Bull. 1991;17:263-87.
11. Duggal HS, Nizamie SH. Novel antipsychotic drugs and INH-related psychosis. Aust N Z J Psychiatry. 2000;34:343-4.
12. DiMartini A. Isoniazid, tricyclics and the “cheese reaction”. Int Clin Psychopharmacol. 1995;10:197-8.
13. Carlsson A. The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology. 1988;1:179-86.
14. Sandyk R, Pardeshi R. Pyridoxine improves drug-induced parkinsonism and psychosis in a schizophrenic patient. Int J Neurosci. 1990;52:225-32.

Singh H, Devi HJ G, Chabaria M, Shekar K. Isoniazid associated psychosis: case series from a tertiary care centre. Open J Psychiatry Allied Sci. 2017 Oct 26. [Epub ahead of print]

Source of support: Nil. **Declaration of interest:** None.