Isoniazid Induced Psychosis: A Case Report

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ABSTRACT

Psychosis is a state of altered behaviour and mentation and it is not common in children. Isoniazid is a commonly used drug in the treatment and prophylaxis of tuberculosis. It may cause psychosis if overdosed but rarely with usual recommended doses. We report a case of drug induced psychosis secondary to isoniazid intake in a seven years old boy, who exhibited psychotic features about 10 days after the commencement of anti-TB combination drugs (Directly Observed Treatment Shortcourse) containing Isoniazid. This patient had no past medical or family history of mental illness. Drug induced psychosis was a possibility, and the responsible drug (isoniazid) was stopped. He improved following the withdrawal of isoniazid. Isoniazid psychosis is a major complication as iatrogenic psychiatric complications can greatly impact the patients’ quality of life, which if recognised early can be effectively treated.

Keywords: adverse effects; isoniazid; psychosis; tuberculosis
INTRODUCTION

Tuberculosis (TB) continues to be an important public health problem. The conventional approaches employed to fight TB are good nutrition, Bacillus Calmette-Guerin (BCG) vaccination, anti-TB therapy. The first line drugs commonly used are Isonicotinic acid hydrazide (INH), Rifampicin, Pyrazinamide, Ethambutol and Streptomycin. INH is also used as prophylaxis. Isonicotinic acid hydrazide (INH), also known as Isoniazid, has been in use since it was introduced by Robitzek in 1952 because of its potency, safety and low cost. INH is a prodrug that must be activated inside M. tuberculosis by the catalase-peroxidase enzyme. Activation is associated with a reduction of the mycobacterial ferric KatG catalase-peroxidase by hydrazine and reaction with oxygen to form an oxy ferrous enzyme complex. Once activated, INH inhibits the synthesis of mycolic acids, an essential component of the bacterial cell wall. The daily recommended INH dosage by World Health Organisation (WHO) for children is 7 – 15 mg/kg/day or 20 mg/kg twice or thrice doses per week or daily, and 5 mg/kg/day for prophylaxis. Adverse effects of INH are commonly seen following both therapeutic use and overdose, and the common side effects of INH are peripheral neuropathy, hepatitis, and rash. Also, headache, poor concentration, weight gain, poor memory, and depression have been associated with INH use. Rarely, psychosis, convulsions, and even death have been reported with conventional doses of this drug, and also, psychosis with obsessive compulsive symptoms (schizo-obssessive disorder).

CASE REPORT

A seven years old boy was admitted to our hospital with complaints of cough, fever since 15 days. The cough was productive, associated with difficulty in breathing. Father gave positive history of contact with TB patient. The patient had received BCG vaccination. He was the first child in a family of four children and there was no past medical or family history of mental illness.

Examination revealed an ill-looking child, appropriate for age, febrile, moderately pale and weighed 20 kg. The patient had tachycardia (178 beats/min), marked respiratory distress with a respiratory rate of 80/min, temperature 101°F, blood pressure 80/40 mmHg and SPO2 of 24%. Child was conscious and oriented. On examination, nasal flaring and digital clubbing were present. There were suprasternal, intercostal and subcostal recessions. There were crepitations in the lower lung zones bilaterally. On per abdomen examination, abdomen was soft non tender, liver was 4 cm palpable below the right costal margin and spleen was non-palpable. Arterial blood gas was sent immediately which was suggestive of hypoxia and saturation was not increased even on high flow oxygen, then the child was immediately intubated and kept on SIMV mode of ventilator.

The patient was resuscitated and treated with intravenous antibiotics and antitubercular drugs (Isoniazid 10 mg/kg, Rifampicin 15 mg/kg, Pyrazinamide 25 mg/kg and Ethambutol 15 mg/kg, all the drugs given daily). Meanwhile basic investigations were done, which were with in...
normal limits. HIV testing and sputum for Acid-Fast Bacilli (AFB) were negative.

Gastric lavage for cartridge based nucleic acid amplification test (CBNAAT) was positive. In MRI tuberculoma were present. Planned extubation was done after 72 hours of admission which was successful and child was kept on oxygen. He was diagnosed as a case of disseminated tuberculosis. Ten days after the commencement of anti-TB, he developed abusive and fearful behaviour, talked excessively and slept poorly. Over the next few days, his condition progressively grew worse and his speech became more excessive, irrational and echolalic. He became restless and unable to sleep (insomnia). Psychiatric opinion was taken and the psychiatric team suspected Isoniazid to be the likely cause of psychosis. Hence, isoniazid was stopped and risperidone, clonazepam and pyridoxine were started. The patient became free of psychotic symptoms over the next two days. After one week, isoniazid was reintroduced at low doses and patient developed symptoms of psychosis again. This confirmed the diagnosis of isoniazid induced psychosis.

**DISCUSSION**

Isoniazid-related psychiatric disorders reported in the literature include psychosis, obsessive-compulsive neurosis, mania and suicidal thought and attempt. The first description of psychotic symptoms due to INH was given by Mandel et al in 1956. Various mechanisms for this phenomenon has been suggested but the exact mechanism is not clearly understood, but INH is known to interfere with several metabolic pathways essential for normal neuronal functioning. INH causes vitamin B6 deficiency by increasing its excretion. INH metabolites inhibit the activation of pyridoxine to pyridoxal 5-phosphate, which is a cofactor of the enzyme glutamic acid decarboxylase that catalyzes the conversion of glutamic acid to gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the central nervous system. The resulting GABA depletion leads to central nervous system dis-inhibition and clinically, isoniazid-induced psychosis or seizures may follow INH overdose. According to the literature, susceptibility increases with old age, personal and family history of psychiatric disorders, malnutrition, alcohol intake, diabetes, renal and hepatic insufficiency, hyperthyroidism etc. The adverse effects are more common among patients in whom pyridoxine is not supplemented; however, they are also known to affect 5% of patients on adequate pyridoxine supplementation (10-50 mg/day). However non administration of pyridoxine was the only identifiable risk factor among these patients.

Another possible reason for acute onset of psychosis may be the pharmacokinetic properties of the drug. INH is rapidly absorbed from the gastrointestinal tract and peak levels are reached within one to two hours after ingestion of a therapeutic dose. It has been found that about 40% of Indian population are slow acetylators, thus causing slow metabolism leading to drug accumulation and thus more side effects. The risk also increases when the dose of INH is above 5 mg/kg, but has also been recorded on low dosage. If the dose of INH was to be calculated based on body weight, then our patient received high dose, which possibly could have increased the susceptibility to the adverse effect.

The usual approach to treat INH induced psychosis is to withdraw the drug, treat the psychosis and then gradually re-introduce INH at a lower dosage after psychosis has completely resolved. Some authors have suggested the use of pyridoxine in high doses following INH challenge, while others have recommended the use of antipsychotics along with high dose pyridoxine. In cases where psychiatric symptoms are not very severe, INH can be continued along with novel antipsychotics like risperidone and olanzapine. In our patient, INH was stopped and patient was treated with a combination of antipsychotics and pyridoxine. However, the presence of a history of drug intake, correlated with the onset of symptoms and their improvement following withdrawal of the drug suggests drug - induced psychosis.

**CONCLUSIONS**

In developing countries, the burden of tuberculosis is huge and the use of antitubercular drugs is increasing. The treating clinician must be aware of
various adverse events following use of isoniazid and should be aware about the drug toxicity profiles of anti-tubercular drugs like INH. Iatrogenic psychiatric complications can greatly impact the patients’ quality of life and physicians’ attitude towards use of INH. Therefore successful control of these complications is crucial.

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