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Isoniazid-Induced Psychosis in 2 Children Treated for Tuberculosis: Case Reports and Literature Review

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SOO, GAO and JOGA managed the patients. Author SOO wrote the draft of the manuscript with help from author GAO. Author OAO managed literature searches and contributed to the correction of the draft. Author JOGA also provided logistic supports. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Aims: To report isoniazid-induced psychosis in 2 children treated for Tuberculosis (TB) as a reminder or an alert to clinicians and other health workers.
Presentation of Cases: Isonicotinic acid hydrazide (INH) is commonly used drug to treat and prevent TB, and because of HIV pandemic, its uses have increased tremendously. This report describes two children aged 14 years and 5 years, who exhibited psychotic features about 9 days and two weeks, respectively after the commencement of anti-TB combination drugs containing INH. These two patients were severely under-nourished, with no past medical or family history of mental

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illness. The psychiatric signs and symptoms resolved completely about 33 days (14-year-old) and 42 days (5 year old) from the time the symptoms started, and 29 days and 28 days, respectively after INH withdrawal and commencement of pyridoxine and haloperidol treatment.
Discussion: Isoniazid-induced psychosis can occur in patients on INH. The time of onset of the symptoms, clinical features, and the drug dosage at which symptoms occur can vary widely. The dose relationship appears to be less significant with psychosis than with peripheral neuritis. The time of onset of symptoms after the institution of INH therapy varies roughly with the dosage, with high doses symptoms appear early, but later with conventional low-dose. The duration of the symptoms and the predisposing factors also differ. Malnutrition, debilitating diseases and past medical or family history of mental illness may act as predisposing factors.
Conclusion: Isoniazid-induced psychosis does occur in children and may present with broad clinical features, even in a patient who may not have past or family history of psychiatric disorders. It can be treated with INH withdrawal, pyridoxine and haloperidol. The severe malnutrition suffered by these two reported cases might have predisposed the patients to INH-induced psychosis.

Keywords: Isoniazid; psychosis; children; tuberculosis.

1. INTRODUCTION

Tuberculosis (TB) continues to be an important public health problem [1], especially in the sub-Saharan African region where poverty, ignorance, natural disasters and Human Immunodeficiency Virus (HIV) infection also, often take their toll on the inhabitants. The conventional approaches employed to fight tuberculosis are good nutrition, Bacillus Calmette-Guerin (BCG) vaccination, anti-TB chemotherapy and chemoprophylaxis. Drug combinations are used to treat TB to prevent drugs resistance and ensure early recovery. Also, TB chemoprophylaxis is recommended to prevent TB disease in people in contact with TB patients, especially immuno-compromised individuals like HIV positive patients. The first line drugs commonly used to treat TB are Isonicotinic acid hydrazide (INH), Rifampicin, Pyrazinamide, Ethambutol and Streptomycin. INH is also used as prophylaxis. INH is, therefore, central to TB chemotherapy and chemoprophylaxis.

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 [2,3]. With the advent of HIV pandemic, the number of TB cases has increased substantially, leading to increasing INH usage [4], and clinical presentation of its adverse reactions. Isoniazid 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, Isoniazid inhibits the synthesis of mycolic acids, an essential component of the bacterial cell wall [5]. The daily recommended INH dosage by World Health Organization (WHO) for children is 7 – 15 mg/Kg/day (up to 300 mg/day) or 20 mg/Kg (maximum of 900 mg per dose) twice or thrice doses per week, and 5 mg/Kg/day for prophylaxis [6].

Adverse effects of isoniazid (INH) are commonly seen following both therapeutic use and overdose, and the common side effects of INH are peripheral neuropathy, hepatitis, and rash [4]. Also, headache, poor concentration, weight gain, poor memory, and depression have been associated with isoniazid use [7]. Rarely, psychosis, convulsions, and even death have been reported with conventional doses of this drug [2], and also, psychosis with obsessive-compulsive symptoms (schizo-obsessive disorder) [8]. The purpose of this paper is to report the occurrence of psychosis in two (2) children who received Isoniazid as part of the treatment for tuberculosis. The aim is to create awareness of the occurrence of INH-induced psychosis among health workers in this era of increased usage of the drug.

2. PRESENTATION OF CASES

2.1 Case 1

A 14-year-old boy admitted to our facility with the history of cough for five years, progressive weight loss of 1 month despite a good appetite, difficulty with breathing of 2 weeks and fever of 4 days. The cough was paroxysmal and productive of yellowish, copious and foul-smelling sputum, with associated drenching night sweats. The

patient did not receive BCG and other childhood vaccines. His father received treatment for a chronic cough. The patient is 4th in a monogamous family of 6 children, and no history of mental ill health in the child or his family. Examination revealed a chronically ill looking patient with severe halitosis, fluffy hairs, dyspnea and pallor. He had digital clubbing, significant peripheral lymphadenopathy, and weighed 22 kg (43.3% of expected). He had tachypnea (46 cycles/min), tachycardia (140 beats/min) and blood pressure of 90/60 mmHg, with the body temperature of 39℃. There were intercostal and subcostal recessions, dullness to percussion, bronchial breath sound with few crepitations on the right hemithorax. The liver was 5 cm palpable and tender.

Diagnosis of pulmonary tuberculosis with lung abscess was made, and other problems identified in the patient were severe undernutrition, anaemia and congestive cardiac failure. The patient was resuscitated, and transfused with blood and placed on intravenous furosemide and antibiotics. He became stable within 72 hours of admission. HIV testing and sputum for Acid-Fast Bacilli (AFB) were negative. The haematocrit was low, and the lymphocytes counts and Erythrocyte sedimentation rate (ESR) were abnormally high. The patient had accelerated reaction to BCG vaccination because there was no Mantoux test kit. Chest X-ray revealed non-homogeneous opacification on the right mid-lower lung zone with multiple cavities having air-fluid levels.

On the eighth day of admission, the patient was started on anti-TB drugs (Isoniazid 13 mg/Kg, Rifampicin 13 mg/Kg, Pyrazinamide 25 mg/Kg and Ethambutol 16 mg/Kg, all the drugs given daily). Nine days after the commencement of the anti-TB, he became unnecessarily elated, talked excessively and slept poorly, although he showed no verbal or physical aggression. Over the next few days, his condition progressively grew worse, and his speech became more excessive, irrational, and echolalic with shouting. He became restless, refused food and drugs and unable to sleep (insomnia). He also had auditory hallucination and impaired judgment. Isoniazid was suspected to be the likely cause of the psychosis, and it was subsequently withdrawn, and Pyridoxine 100 mg/day was commenced. He continued the other three anti-TB drugs. Mental health team was invited, and the team made an assessment of organic mental disorder (psychosis) and prescribed Haloperidol 2.5 mg nocte. Medications were given via nasogastric tube because the patient refused to swallow.

Seven days following the withdrawal of isoniazid and commencement of pyridoxine and haloperidol, the patient symptoms began to subside, and he started to accept food and medications. Over the next few weeks, his medical condition and mental state continued to improve. Twenty-three (23) days after the appearance of psychiatric symptoms and commencement of treatment, his progress was described as being satisfactory by both Paediatricians and Psychiatrists. He was therefore allowed home to continue his drugs and to be followed-up in out-patient clinics.

On his first follow-up clinic visit, two weeks after discharge, all psychiatric symptoms were said to have resolved completely about four days earlier. His medical condition also improved, and he weighed 30 Kg (59.1% of expected). He was to continue his anti-TB and haloperidol. His next follow-up clinic visit coincided with the completion of the active phase (2 months) of anti-TB drugs. Pyrazinamide and Ethambutol were discontinued, and Rifampicin was continued, with the re-introduction of Isoniazid at a lower dosage (5 mg/Kg/day). The re-introduction of Isoniazid did not cause re-occurrence of any psychiatric symptoms.

2.2 Case 2

A 5-year-old girl was admitted to our hospital with complaints of weight loss, recurrent fever and cough for four months. The cough was productive of sputum, with associated difficulty in breathing. Mother denied any history of contact with Tuberculosis patient. The patient received BCG vaccination. She is the first child in a family of 3 children and no past medical or family history of mental illness. Examination revealed a chronically ill-looking child, small for age, febrile, moderately pale, and weighed 10 Kg (55.6% of expected). The patient had tachycardia (160 beats/min), with first and second heart sounds and pansystolic murmur heard. Also, she had respiratory distress, with a respiratory rate of 80 cycles/min. There were crepitations in the lower lung zones bilaterally. The liver was 10 cm palpable, soft and tender, and spleen 4 cm.

The diagnosis of failure to thrive secondary to Pulmonary Tuberculosis, with HIV infection as a differential, was made. Other diagnoses made were severe under-nutrition, ventricular septal

defect and bronchopneumonia in heart failure. The results of investigations showed that the patient is HIV seropositive, had low haematocrit, elevated lymphocytes count but low CD4+ (10%). Chest x-ray revealed upper lobe collapse with lower lobe showing pneumonic changes. The patient was managed with oxygen, frusemide, blood transfusion and intravenous antibiotics. She was discharged a week after admission and referred to HIV clinic for further management.

She was referred from the HIV clinic to the chest clinic, where anti-TB therapy was commenced as follows: Isoniazid 5 mg/Kg, Rifampicin 10 mg/Kg, Pyrazinamide 26 mg/Kg and Ethambutol 17 mg/Kg, all given daily. Two weeks after the commencement of the anti-TB drugs, the mother noticed that the child was behaving irrationally, scratching the whole of her body. She walked out of the house roaming aimlessly about and even went to cut her hairs without her parents' knowledge or consent. She was sometimes so disoriented that she would not know her name.

The anti-TB regimen was reviewed, and Ethambutol was withdrawn. Two weeks later in the follow-up clinic, the mother still complained about the child's irrational behavior. Patient and her anti-TB regimen were further reviewed, and a diagnosis of Isoniazid-induced psychosis was made, with delirium as a differential. Isoniazid was withheld, and Ethambutol re-introduced, and to continue pyrazinamide and rifampicin. She was given two weeks appointment. However, she did not honour the appointment. She was seen six weeks after isoniazid was withdrawn and mother said that all the irrational behaviours had disappeared about two weeks earlier. She now related well and responded well to commands; also clinically, she looked better.

3. DISCUSSION

Isoniazid-related psychiatric disorders reported in the literature include psychosis, obsessive-compulsive neurosis, mania [8,9] and suicidal thought and attempt [4]. The mechanism by which INH induces psychosis and other related disorders is not clearly understood [3]. The drug is known to interfere with various metabolic pathways essential for neuronal functioning. INH causes vitamin B6 deficiency by increasing its excretion. INH metabolites inhibit the activation of pyridoxine to pyridoxal 5-phosphate. Pyridoxal 5- phosphate 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 [5]. The resulting GABA depletion leads to central nervous system dis-inhibition and, clinically, isoniazid-induced psychosis or seizures may follow INH overdose [4,5]. Advanced age, alcohol intake, diabetes, family history of mental illness, malnutrition and hepatic insufficiency increase susceptibility to isoniazid-induced psychosis [2].

Malnutrition is one of the predisposing factors in INH-induced psychosis. Our patients had severe malnutrition and weighed 43.3% and 55.6% of expected weight for their ages. The severe malnutrition suffered by these two reported cases might have predisposed the patients to INH-induced psychosis. Malnutrition is caused by the deficiency of nutrients, especially amino acids necessary for healthy body function. Amino acids are needed to make various neurotransmitters in the central nervous system. Pyridoxine deficiency may play a role in the pathogenesis of isoniazid-induced psychosis, such deficiency states may be detected indirectly by measuring urinary metabolites of tryptophan [9]. Some authors hold the view that a history of psychiatric illness is essential for the development of INH psychosis while others feel that it can occur in a healthy person with no previous history [10]. None of our patients had any medical or family history of mental illness.

There is considerable variability in the clinical features of INH-induced psychosis in the literature [2]. Agarwal et al. in [11], reported symptoms of restlessness, irritability, emotional instability, agitation, apprehension, and fluctuation in behavior after isoniazid therapy. These features were similar to the one seen in the two patients we are reporting. Also, INH-induced psychosis may present with inappropriate actions, argumentative behavior, mental depression, euphoria, grandiose ideas and complex delusions [12].

In INH-induced psychosis, the onset and the duration of psychotic symptoms vary widely. Gaur et al. reviewed reported cases of INH-induced psychosis and found that the appearance of psychiatric symptoms occurred as early as two days after starting INH (range: two days to 10 months) [12,13]. The duration of psychotic symptoms in reported cases in literature varied, 3 days [13], 7-45 days [12], and 120 days [11]. Our patients' time of onset and

duration of psychotic features are similar to the above stated periods.

Available literature has been silent on the relationship between psychosis and INH dosage. The dose relationship appears to be less significant with psychosis than with peripheral neuritis [14]. The time of onset of symptoms after the institution of INH therapy varies roughly with the dosage. With high doses of INH, symptoms often appear within three to five weeks [14]. In patients receiving conventional low-dose INH therapy, symptoms usually do not appear until six months [9]. The neurologic toxicity does not seem to be entirely dose or duration related [15]. It can occur even with a conventional single dose or within days [13], as observed in case 1, or may take weeks as in case 2 or months to appear [15]. INH-induced psychosis poses a great clinical dilemma to physicians regarding whether to continue the drug or not, as INH is the most important drug for treating and preventing tuberculosis [10]. The usual approach is to stop INH, treat the psychiatric disorders and gradually re-introduce INH at lower dosage after the mental disorder has completely resolved.

4. CONCLUSION

INH- induced psychosis does occur, even in children. It may occur more frequently because of increased INH usages nowadays. It can occur in patients that have no medical or family history of mental illness. Therefore, clinicians and other health workers should observe precautionary measures and be on the look-out while prescribing Isoniazid, especially to patients that have predisposing factors like family history of mental illness, malnutrition and debilitating diseases. We are of the opinion that, the severe malnutrition suffered by these two patients might have predisposed them to INH-induced psychosis. Moreover, if psychiatric disorder occurs, the drug should be withdrawn, give pyridoxine and treat the mental disorder. INH may be re-introduced at low dose after the symptoms have resolved completely.

CONSENT

All authors declare that verbal informed consent was obtained from the parents of the patients (cases 1 and 2) for publication of these case reports.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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