

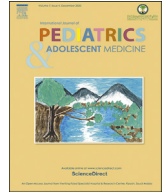
HOSTED BY



ELSEVIER

Contents lists available at ScienceDirect

## International Journal of Pediatrics and Adolescent Medicine

journal homepage: <http://www.elsevier.com/locate/ijpam>

## Acute psychosis secondary to isoniazid in pediatric pulmonary tuberculosis: A case report and literature review

Saleh Alfawaz <sup>a</sup>, Nadia Alattas <sup>a,b</sup>, Moza Alhammadi <sup>b,\*</sup>, Saadia Waqar <sup>b</sup>, Sulaiman Al Alola <sup>b</sup><sup>a</sup> College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia<sup>b</sup> Division of Pediatric Infectious Diseases, King Abdullah Specialized Children's Hospital (KASCH), National Guard Health Affairs, Riyadh, Saudi Arabia

## ARTICLE INFO

## Article history:

Received 19 August 2019

Received in revised form

15 November 2019

Accepted 17 March 2020

Available online 5 April 2020

## Keywords:

INH-Induced psychosis

Isoniazid

Hallucinations

Psychosis

Tuberculosis

Pediatrics

## ABSTRACT

Isoniazid (INH) is a first-line tuberculosis (TB) drug and is currently recommended as part of active and latent TB treatment in all ages. INH adverse reactions range from mild hepatitis to severe neurological symptoms and psychosis. Since its introduction in the 1950s, many case reports have explored INH-induced psychosis. We describe a 12-year-old girl with acute onset hallucinations and delusions as a rare complication of INH and review previous case reports and identified risk factors. Pediatricians need to be aware of this less common side effect as they work through a differential of acute psychosis in children.

© 2020 Publishing services provided by Elsevier B.V. on behalf of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Tuberculosis (TB) is one of the leading causes of mortality and is estimated to infect one in every three individuals worldwide [1]. The World Health Organization (WHO) recommends a combination treatment of four drugs for two months (isoniazid (INH), rifampicin, pyrazinamide, and ethambutol), followed by two drugs (INH and rifampicin) for 4 months as first line therapy for newly diagnosed pulmonary TB in both pediatric and adult patients [2]. This regimen is generally considered efficacious, safe, and cost-effective. However, adverse effects and drug interactions often complicates the treatment of tuberculosis.

INH is used in treating active and latent TB infections. In adults, the recommended dose is 5mg/kg/day with a maximum of 300 mg/day [2]. In the pediatric population, the recommended range is 7–15mg/kg/day with a maximum of 300mg/day [3,4]. INH has common side effects that need to be explained to patients and

assessed for on clinic follow up. These include elevated hepatic transaminases or hepatitis, nausea, vomiting, peripheral neuropathy related to vitamin B6 deficiency, and dermatitis [2,3,5]. Shortly after INH was introduced as an antitubercular agent in 1952, reports of cases exhibiting psychotic symptoms as adverse effects were published [6,7]. Since then, multiple publications have addressed INH-induced psychosis and explored the associated risk factors [6,8,9]. Other antitubercular agents have been linked to neurotoxicity and psychosis such as cycloserine, ethionamide, ciprofloxacin, and ethambutol [6,10]. However, INH is frequently prescribed, and its side effects have the potential to impact a higher number of TB patients in general.

Only recently has the international literature identified cases of INH-induced psychosis within the pediatric population [11]. Pediatricians assessing children on antitubercular therapy in an emergency room or in a clinic setting need to be aware of this adverse effect. We report a case of a 12-year-old, HIV-seronegative girl who presented with delusions and hallucinations after starting TB therapy and review the literature on INH-induced psychosis.

## 2. Case

A 12-year-old previously healthy Saudi girl was diagnosed with

\* Corresponding author. Division of Pediatric Infectious Diseases, King Abdullah Specialized Children's Hospital, National Guard Health Affairs, Riyadh, Saudi Arabia. E-mail address: [Mozahammadi@gmail.com](mailto:Mozahammadi@gmail.com) (M. Alhammadi).

Peer review under responsibility of King Faisal Specialist Hospital & Research Centre (General Organization), Saudi Arabia.

pulmonary TB based on a two-week history of fever, cough, and weight loss, and a sputum culture positive for *Mycobacterium tuberculosis*. She was started on an antitubercular regimen of rifampicin, INH, pyrazinamide, and ethambutol. Pyridoxine (vitamin B6) supplement, was not prescribed. Two weeks after initiating her TB therapy, she presented to the Emergency Department with frequent episodes of vomiting, loss of appetite, decreased activity, and behavioral changes that had intensified over one week. She presented with emotional lability, self-talk, visual, tactile, and auditory hallucinations, and somatic delusions. She had no history of fever, headaches, abnormal movements, recent travel, previous medical or psychiatric illnesses, or family history of psychiatric disorders. She denied consuming any other medicinal agents and reported adherence to her TB medications. She was on INH 10mg/kg/day, rifampicin 15mg/kg/day, ethambutol 20mg/kg/day, and pyrazinamide 30mg/kg/day.

On physical examination, her weight was 24 kg with a body-mass index (BMI) of 11.98 kg/m<sup>2</sup>. She had normal vital signs, scattered lung crepitations on respiratory exam, and a normal neurological evaluation. Her lab results, including cell counts and serum electrolytes, were within normal values. An initial toxicology screen was not carried out. With the acute onset of symptoms and behavioral changes, brain imaging and cerebrospinal fluid (CSF) studies were requested to evaluate for extra-pulmonary tuberculosis involving the central nervous system (CNS). CSF analysis including cell counts and protein and glucose levels were normal, with negative bacterial culture, mycobacterial culture, and TB PCR. MRI of the brain was normal. Sputum stain for acid fast bacilli was positive and a chest x-ray demonstrated bilateral apical multiple cavitory lesions. HIV serology was negative. Neurology and psychiatric evaluations were conducted and medication-induced side effects including INH-related psychosis was considered. For this reason, INH was stopped and replaced with moxifloxacin (a second-line TB agent).

Pyridoxine was added to her therapy at a dose of 25 mg/day, and she was started on risperidone 0.5 mg/day. She remained admitted for observation for a week, during which time, her hallucinations and abnormal behavior gradually stopped. She was discharged on rifampicin, ethambutol, moxifloxacin, pyrazinamide, pyridoxine, and risperidone. On follow up in clinic after two weeks, there was complete resolution of her psychiatric symptoms. Pyridoxine and risperidone were both discontinued. After completing 2 months of the four-drug TB regimen, she was switched to a two-drug regimen of rifampicin and moxifloxacin for four months. Follow up evaluations confirmed complete resolution of respiratory symptoms, AFB-negative sputum smear and culture, adequate weight gain and recovery of appetite, improvement in her chest x-ray changes, and no recurrence of abnormal behavior or hallucinations.

### 3. Discussion

Psychosis is a rare adverse effect of INH. Older reports place the incidence of psychiatric symptoms at 1.9% from a US surveillance program in the 1970s and 1% in a review of cases of TB in Peru between 1991 and 1999 [6]. No recent surveys have been conducted. Behavioral and mood alterations, problems with memory, concentration and communication, sleep and appetite disturbances, and hallucinations and delusions have been described [6,8,12].

Most reports are from the adult population. Onset of psychosis is within days to months from drug initiation, with the majority developing symptoms in the first two weeks [8–10,12,13]. A typical storyline tends to occur in most reported cases with a recurring temporal association. The patient presents with convincing symptomatology, is diagnosed with pulmonary TB, is then started on

combination therapy including INH, and then subsequently develops new and acute onset psychiatric symptoms which resolve once INH is discontinued. Patients were reportedly on standard recommended adult doses (300 mg/day) [8,13,14]. Pyridoxine prescription and dosing varied. Many received anxiolytics and or antipsychotics initially [8,12–15]. The time from discontinuation to complete resolution of symptoms ranged from 7 days to 120 days [8,10].

Oninla et al. report two pediatric cases in undernourished children [11]. In the first case, a 14-year-old, severely undernourished boy developed auditory hallucinations, echolalia, food refusal, and insomnia eight days after starting TB therapy for extensive pulmonary disease. He received 13mg/kg/day of INH without a vitamin B6 supplement. After discontinuing INH and starting vitamin B6 (100 mg) and haloperidol, his symptoms gradually improved. Two months later, INH was reintroduced at 5mg/kg/day with no recurrence of symptoms. Their second case was of a 5-year-old girl who was HIV positive with failure to thrive and severe malnutrition. She developed disorientation and bizarre behaviors (scratching her body, attempting to cut her hair, wandering aimlessly) two weeks after starting TB therapy (with INH at 5mg/kg/day). An initial attempt to stop ethambutol did not improve her condition and only when INH was stopped did her symptoms resolve. In her case, she did not receive vitamin B6, anxiolytics, or antipsychotics and INH was not reintroduced.

A few reports describe INH-associated psychosis in patients on INH prophylaxis therapy for latent TB. Sharawat et al. report a 3-year-old girl who developed episodes of aggression, social withdrawal, and what is thought to be visual hallucinations two weeks after starting INH (10 mg/kg/day) as prophylaxis for a confirmed household case of pulmonary TB [16]. Iannaccone et al. describe a 14-year-old girl who, one day after starting latent TB therapy (INH 300 mg and pyridoxine 50 mg), developed auditory hallucinations that urged her to attempt suicide by drug overdose [17]. She did not receive an antipsychotic agent initially and follow up psychiatric evaluation after discontinuing INH revealed no previous psychiatric illness and no recurrence of psychiatric symptoms or suicidal ideation.

Identified risk factors for psychosis include age greater than 50 years, malnutrition, uremia, diabetes mellitus, hepatic insufficiency, hyperthyroidism, and personal or family history of psychiatric illness [6,9,18]. In their case series, Menon et al. highlighted the influence of malnutrition when they presented a 35 year-old woman, a 55 year-old man, and a 60 year-old man who all developed INH-induced psychosis with documented body-mass indices of 13, 18, and 16.8 kg/m<sup>2</sup> respectively [8]. In these cases, the standard dose of 300mg was equivalent to > 5mg/kg/day. Oninla et al. also present pediatric cases with severe undernutrition [11]. Our patient had a BMI of 11.9kg/m<sup>2</sup> and was below the 5th percentile for age and sex. Additionally, the rate of acetylation can affect INH metabolism and may also be a factor that influences the risk of psychosis [8,17]. Acetylation is genetically determined and occurs with racial differences, but cannot be routinely tested on an individual basis. Slow acetylation can result in drug accumulation and may be a pharmacokinetic risk factor.

Vitamin B6 supplement is recommended with the initiation of TB therapy in certain populations at risk of vitamin deficiency (pregnancy, HIV seropositive, renal failure, diabetes mellitus, and malnutrition), to avoid peripheral neuropathy [2]. The WHO recommends a dose of 10 mg/day [2]. Children with malnutrition or with HIV on antiretrovirals are considered at risk and are recommended to receive 5–10 mg/day [4] or 1mg/kg/day [3]. Despite several authors reporting supplementing from the beginning of treatment [8,13,14] or starting higher doses (40–100mg/day) at the time of psychotic symptomatology [9,11], there has not been a clear

association between vitamin B6 deficiency and INH-induced psychosis at this point.

The mechanism of INH-induced psychosis is not fully understood. Common theories suggest a relation to interference with neurotransmitters. INH is a monoamino oxidase inhibitor and thus can result in elevated levels of catecholamines and serotonin [13,19]. Also, through oxidative stress, it can reduce N-methyl D-aspartate receptors (NMDAR), affecting memory and learning and contributing to psychosis [9]. Through the excretion and the depletion of pyridoxine, INH can also affect the levels of tryptophan and serotonin [8]. And through the inhibition of pyridoxine activation, it decreases the levels of gamma-aminobutyric acid (GABA), an important inhibitory neurotransmitter [9].

Psychosis in children is rare and it is important to evaluate the differential diagnosis before concluding an iatrogenic drug-induced cause. This includes ruling out infectious or autoimmune encephalitis, seizure disorder, tumors, endocrinopathies, and toxic agents among other differentials [16]. Excluding alternative causes along with the temporal correlation of symptoms and drug ingestion/cessation strengthens the likelihood of causality. Menon et al. and Prasad et al. increased the plausibility of causality by attempting to reintroduce INH which resulted in the recurrence of psychiatric symptoms. In Oninla et al.'s first described pediatric case, INH was reintroduced with no recurrence of psychiatric symptoms [11]. However, the dose was modified to 5mg/kg/day and the reintroduction occurred two months after initial presentation. This may have provided adequate time for any risk factors such as malnutrition or comorbidities to improve or resolve, and thus could have altered his risk. This was not expanded on by the authors. Using the Naranjo criteria for adverse reactions, we were able to conclude that INH-induced psychosis in our patient was 'probable' and not 'definitive', since we did not re-challenge her with INH to assess symptoms recurrence and we did not have an objective method to confirm the diagnosis [20].

There is no consensus on how patients suspected to have INH-induced psychosis should be managed. The majority consider stopping INH the most important step. Most reports include the initial addition of anxiolytics and antipsychotics in order to manage acute symptoms, though the duration of such medications varied from days to months. For a patient presenting with acute onset psychosis who has recently been started on INH and who is suspected of having INH-induced psychosis, we recommend discontinuing INH, as long as there are alternative choices for TB therapy. The role of pyridoxine remains unclear and the option to give a daily dose is left up to the treating physician. Short courses of anxiolytics and antipsychotics can help alleviate initial symptoms. Input from the infectious diseases services, pediatric psychiatry, and neurology is strongly recommended for diagnosis, management, and follow up.

#### 4. Conclusion

We report a case of acute onset psychiatric symptoms in a pediatric patient with a temporal association strongly supporting INH-induced psychosis. As INH is one of the major first line drugs in treating active and latent TB, pediatricians need to be aware of this rare adverse effect. Although, it remains a diagnosis of exclusion, considering INH-induced psychosis and discontinuing INH in a timely fashion can help bring an early resolution to psychiatric symptomatology and relief for the patient and parents.

#### Authors' contributions

All authors contributed equally to this case management and report writing.

#### Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

#### Declaration of competing interest

The authors report no conflict of interest.

#### References

- [1] Who | 3. Tuberculosis control. n.d. [https://www.who.int/trade/distance\\_learning/gpgh/gpgh3/en/index4.html](https://www.who.int/trade/distance_learning/gpgh/gpgh3/en/index4.html) (accessed November 7, 2019).
- [2] Who. Guidelines for treatment of tuberculosis. <https://www.who.int/tb/publications/2010/9789241547833/en/>. n.d (accessed November 7, 2019).
- [3] Kitai I, Demers A-M. Chapter 9: Canadian tuberculosis standards 7th edition: 2014 – pediatric tuberculosis - Canada.ca. <https://www.canada.ca/en/public-health/services/infectious-diseases/canadian-tuberculosis-standards-7th-edition/edition-21.html#s7-2>. n.d (accessed November 8, 2019).
- [4] Treatment of TB in children - Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children - NCBI Bookshelf n.d. <https://www.ncbi.nlm.nih.gov/books/NBK214449/#ch4.s3> (accessed November 8, 2019)
- [5] Sb B. *Journal of Drug Design and Research* Cite this article: Bhise Sb. Isoniazid Toxicity 2017;4. 2017.
- [6] Pachi A, Bratis D, Moussas G, Tselebis A. Psychiatric morbidity and other factors affecting treatment adherence in pulmonary tuberculosis patients. *Tuberc Res Treat* 2013;2013:1–37. <https://doi.org/10.1155/2013/489865>.
- [7] Jackson SLO. Psychosis due to isoniazid. *Br Med J* 1957;2:743–6. <https://doi.org/10.1136/bmj.2.5047.743>.
- [8] Menon VB, Shaji R, Pereira P, Chikkaveeriah SK, Ramesh M. Case Series Isoniazid Associated Psychosis: A Case Series of 3 Patients. *Indian J Pharm Pract* n.d.;10. <https://doi.org/10.5530/ijopp.10.2.29>.
- [9] Sharma A, Agarwal S, Dabral A, Khirime D, Rawat R, Babbar A, et al. Isoniazid induced psychosis. vol. vol. 4. [n.d].
- [10] Prasad R, Garg R, Verma S. Isoniazid- and ethambutol-induced psychosis. *Ann Thorac Med* 2008;3:149–51. <https://doi.org/10.4103/1817-1737.43083>.
- [11] Oninla S, Oyedeji G, Oninla O, Gbadebo-Aina J. Isoniazid-induced psychosis in 2 children treated for tuberculosis: case reports and literature review. *Int J Med Pharm Case Reports* 2016;6:1–6. <https://doi.org/10.9734/ijmpcr/2016/23675>.
- [12] Gomes J, Durães D, Sousa A, Afonso H. Isoniazid-induced acute psychosis in a patient with pleural tuberculosis. *Case Rep Psychiatry* 2019;2019:1–3. <https://doi.org/10.1155/2019/4272941>.
- [13] Arya S, Sukhija G, Singh H. Acute psychosis after recent isoniazid initiation. *J Clin Diagn Res* 2015;9. <https://doi.org/10.7860/JCDR/2015/12450.6130.VD01-2>.
- [14] Alao AO, Yolles JC. Isoniazid-induced psychosis. *Ann Pharmacother* 1998;32:889–91. <https://doi.org/10.1345/aph.17377>.
- [15] Verma S, Sharma PK, Sivanandan S, Rana N, Saini S, Lodha R, et al. Spectrum of primary immune deficiency at a tertiary care hospital. *Indian J Pediatr* 2008;75:143–8. <https://doi.org/10.1007/s12098-008-0022-9>.
- [16] Sharawat IK, Dawman L. Toddler with intermittent abnormal behavior. *Pediatr Emerg Care* 2018;1. <https://doi.org/10.1097/pec.0000000000001555>.
- [17] Iannaccone R, Sue YJ, Avner JR. Suicidal psychosis secondary to isoniazid. *Pediatr Emerg Care* 2002;18:25–7. <https://doi.org/10.1097/00006565-200202000-00008>.
- [18] Pallone KA, Goldman MP, Fuller MA. Isoniazid-associated psychosis: case report and review of the literature. *Ann Pharmacother* 1993;27:167–70. <https://doi.org/10.1177/106002809302700205>.
- [19] James Bourgeois MA, Zelenka M. Case report psychotic disorder associated with isoniazid, vol. 161; 1996.
- [20] 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. <https://doi.org/10.1038/clpt.1981.154>.