

## An unusual case of focal seizures after a therapeutic dose of isoniazid: a case report

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### Abstract

Tuberculosis remains a major cause of morbidity in endemic areas. Isoniazid (INH) is an important first-line agent for its treatment. Its major adverse effects include hepatotoxicity and neurotoxicity. Neurological side effects usually occur at toxic doses; however, few cases have reported generalized seizures at therapeutic doses. Focal seizures after therapeutic doses are rare. Here, we present the case of a 78-year-old male diagnosed with squamous cell carcinoma of the lung and pulmonary tuberculosis who experienced focal seizures after INH administration. No structural, metabolic, or infectious cause was found. The seizures stopped after discontinuation of the drug, which confirmed the diagnosis.

**Key words:** tuberculosis, anti-tubercular therapy, isoniazid, focal seizures, adverse drug reaction.

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### Introduction

Pakistan is an endemic area for tuberculosis, ranking fifth among the high-burden countries worldwide. An estimated 510,000 new cases emerge each year.<sup>1</sup> Isoniazid (INH) is a first-line agent for the treatment of tuberculosis (as a part of fixed-dose combination therapy) and also for latent tuberculosis (as monotherapy or part of combination therapy). The recommended dose of INH in adults is 5 mg/kg with a maximum dose of 300 mg daily or 15 mg/kg with a maximum dose of 900 mg once, twice, or three times per week.<sup>2</sup> Its major adverse effects include hepatitis and peripheral neurotoxicity, which is usually dose-related. Seizures, however, are rarely reported at conventional doses.<sup>3</sup> Ingestion of high doses of INH can cause metabolic acidosis, seizures, and even coma in severe cases.<sup>4</sup> Very few cases of seizures occurring at therapeutic doses have been reported, out of which generalized tonic-clonic seizures were seen predominantly.<sup>5-7</sup> Focal seizures are very rarely seen in patients taking isoniazid, with only two documented cases reported, to the best of our knowledge.<sup>8-9</sup> This report presents a case of focal seizures occurring at the therapeutic dose of INH administered to a patient who had pulmonary tuberculosis along with squamous cell carcinoma of the lung. Physicians need to recognize this rare side effect when managing patients presenting with focal seizures while taking Anti-Tubercular Therapy (ATT) at therapeutic doses, in order to make an early diagnosis.

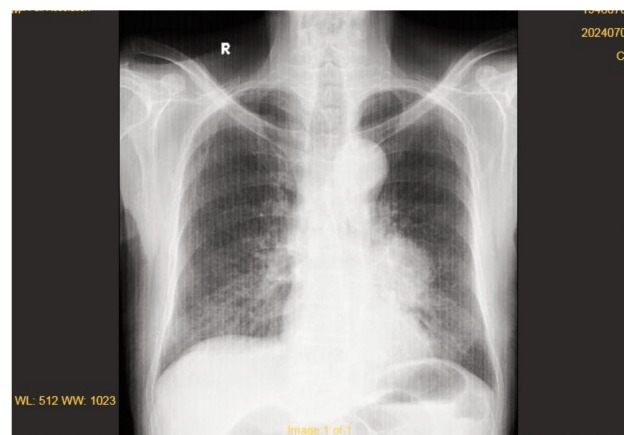
### Case Report

Our patient was a 78-year-old male ex-smoker with hypertension and Chronic Obstructive Pulmonary Disease (COPD). Both were well controlled on regular treatment, which included amlodipine 10 mg for hypertension and budesonide+formoterol inhaler 400+6 mcg for COPD. He visited the outpatient clinic with complaints of gradually worsening shortness of breath for 2 weeks with no other associated symptoms. A chest radiograph was done, which showed homogenous opacity in the left peri-hilar region, which was not present on the last follow-up 4 months ago (Figure 1). A contrast-enhanced computed tomography of the chest was ordered, which showed a soft tissue density lesion in the left hilar region measuring approximately 74x72x62 mm and giving heterogeneous enhancement (Figure 2). A bronchoscopy was performed to obtain a biopsy sample; however, no endobronchial lesion was identified. The bronchoalveolar lavage sample was sent for infective workup and cytology, all of which were negative. *Mycobacterium tuberculosis* was detected on Genexpert *Mycobacterium tuberculosis*-Rifampicin Resistance (MTB-RIF) assay. An ultrasound-guided trucut biopsy was performed, revealing cells with markedly pleomorphic hyperchromatic nuclei and eosinophilic cytoplasm. Immunohistochemical stains were positive for p40 and negative for Thyroid Transcription Factor-1 (TTF-1). The above findings were consistent with squamous cell carcinoma. The patient was started on ATT according to the recom-

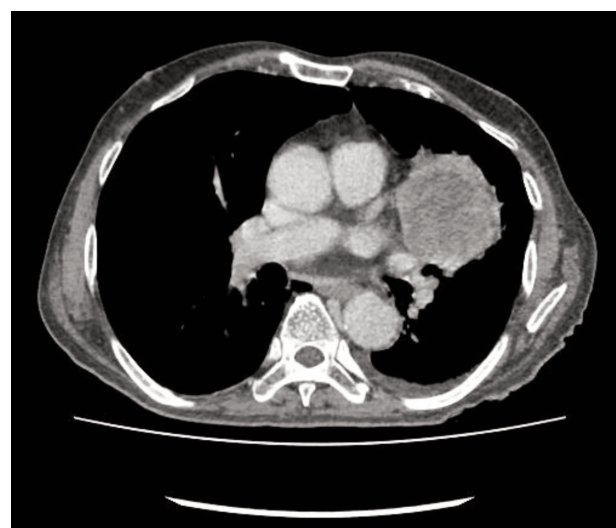
mended fixed-dose regimen with a body weight of 65 kg (which consisted of pyrazinamide 1600 mg, ethambutol 1100 mg, rifampicin 600 mg, INH 300 mg) along with pyridoxine 50 mg, and he was referred to an oncologist for further management plan. Eleven days later, the patient was brought to the emergency department after experiencing facial twitching, facial spasms, and sustained jerky movements of the left upper limb with impaired consciousness, suggestive of focal seizures. He had no previous history of epilepsy. On clinical examination, he was conscious but lethargic, with vitals within normal range. Neurological examination was unremarkable except for confusion, and there was no focal deficit. He was loaded with intravenous levetiracetam 1 gm and was admitted with the suspicion of seizure activity secondary to possible brain metastases. Routine blood tests (complete blood count, renal function tests, serum electrolytes, serum calcium) were all within normal limits, which ruled out metabolic causes of seizures. Magnetic Resonance Imaging (MRI) of the brain with contrast was negative for any abnormal intracranial enhancement (Figure 3). The patient's routine medications were continued along with ATT and pyridoxine. On the first evening after admission, he again had a similar episode of focal seizure. He was loaded with a further 1 gm of intravenous levetiracetam. Electroencephalography was performed, which showed ongoing seizure activity, and was aborted after loading the patient with intravenous phenytoin at 10 mg/kg. Cerebrospinal Fluid (CSF) was sent for a detailed report, culture, and sensitivity which was later reported normal. The patient continued to have similar seizures despite being on intravenous levetiracetam (1 gm twice a day), phenytoin (100 mg twice a day), and lacosamide (100 mg twice a day). A suspicion of INH-induced seizures was raised; hence, ATT was stopped while continuing pyridoxine at 50 mg once daily. The patient had an improvement in overall consciousness level and had no further episodes of seizure after stopping INH, thereby confirming our diagnosis. The Hartwig Scale was used for severity assessment of adverse drug reactions, and our patient was in the category of level 4, which is moderate in severity.<sup>10</sup> According to the World Health Organization – Uppsala Monitoring Center (WHO-UMC) system for causality assessment, the reaction was probable/likely due to INH.<sup>11</sup> Since the patient remained seizure-free, he was discharged with a referral to oncology for further management of the squamous cell carcinoma. A plan was made to restart ATT with the combination of pyrazinamide 25 mg/kg, rifampicin 10 mg/kg, and ethambutol 15 mg/kg for 2-3 months, depending on treatment response.

## Discussion

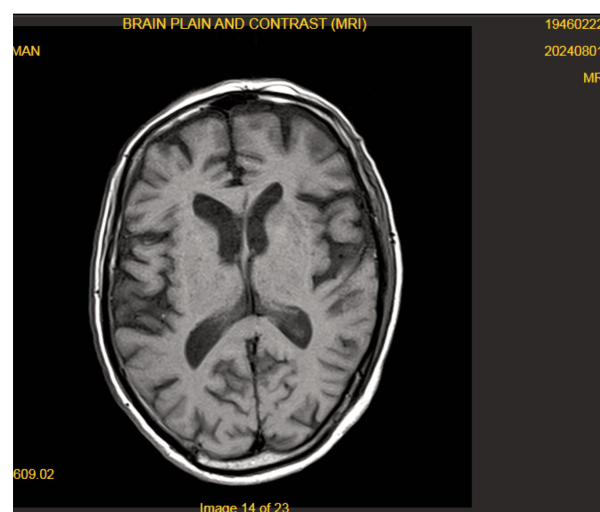
Isoniazid is a widely prescribed antimicrobial for the treatment of tuberculosis. It primarily causes hepatotoxicity; however, neurological side effects are also observed, with severe symptoms usually occurring at toxic doses.<sup>3</sup> Our patient presented with the primary diagnosis of lung carcinoma while concomitantly diagnosed with pulmonary tuberculosis. When he presented with an episode of focal seizure, metastatic disease was our initial differential diagnosis, as he did not have any previous history of epilepsy. A metabolic profile and brain imaging were performed, both of which revealed no abnormal findings. CSF studies were also normal, effectively ruling out Central Nervous System (CNS) infection. The patient's in-hospital treatment included ATT, anti-epileptics drugs, as mentioned above, and amlodipine for his blood pressure control. During the course of treatment, no drug-drug interactions occurred, which might have contributed to the seizures. Despite treatment with mul-



**Figure 1.** Chest radiograph showing homogenous opacity in the left perihilar region.



**Figure 2.** A contrast-enhanced computed tomography of the chest showing a soft tissue density lesion in the left hilar region measuring approximately 74x72x62 mm and giving heterogeneous enhancement.



**Figure 3.** Magnetic Resonance Imaging (MRI) of the brain showing no abnormal findings to explain the convulsions.



multiple anti-epileptic drugs, our patient did not improve, raising the suspicion of INH-induced focal seizures. It was decided to discontinue ATT, and no further seizures occurred after discontinuation of the drug, thereby confirming our diagnosis. Isoniazid is associated with neurological side effects, including paresthesia, peripheral neuropathy, dysarthria, irritability, restlessness, headache, dysphoria, psychosis, and seizures with undefined frequency.<sup>6</sup> A syndrome of seizures, metabolic acidosis, coma, and even death can occur at toxic doses. The exact mechanism for the development of convulsions at the therapeutic dose of isoniazid remains a subject of debate. A presumed etiology of INH-induced seizures involves a reduced availability of Gamma-Aminobutyric Acid (GABA), which is the major inhibitory neurotransmitter in the central nervous system. Isoniazid metabolites inhibit pyridoxine phosphokinase which is responsible for converting pyridoxine to its active form, pyridoxal-5-phosphate. Pyridoxal-5-phosphate is a co-factor for glutamic acid decarboxylase enzyme required for the synthesis of GABA. The consequent reduction in GABA results in increased susceptibility to seizures. Co-administration of pyridoxine is always recommended with isoniazid. Prolonged use of isoniazid may result in pyridoxine deficiency, which can subsequently lead to the development of seizures.<sup>8</sup> Drug-induced seizures are commonly associated with toxic overdoses,<sup>4</sup> with occurrences at therapeutic doses of isoniazid reported in only a few cases. A review of the literature on INH-induced seizures at therapeutic doses reveals notable variations in both the type of seizures and their onset times following the initial dose. To our knowledge, only two documented cases of focal seizures have been reported,<sup>8-9</sup> whereas most cases involved generalized tonic-clonic seizures following therapeutic doses of isoniazid. Asnis DS *et al.* reported a case of a 66-year-old female who developed focal seizures 48 hours after initiation of isoniazid treatment for latent tuberculosis infection.<sup>8</sup> Mohammad *et al.* described a case of a 5-year-old female who, after starting an isoniazid combination regimen for abdominal tuberculosis, experienced hemi-clonic seizures 14 days into the treatment.<sup>9</sup>

## Conclusions

Physicians should be aware of the possibility of isoniazid-induced seizures in patients on ATT who present with convulsions, even at therapeutic doses. The decision to continue or discontinue the ATT can significantly impact the course and morbidity of the disease. Patients presenting with first-ever seizures should be thor-

oughly investigated for all the possible metabolic or infective causes while keeping in mind the co-morbidities, drug history, and concurrent illnesses when making differential diagnoses. This approach will facilitate early and accurate management, ultimately improving overall patient outcomes.

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