An unusual case of seizures in a 5-year-old Syrian female with abdominal tuberculosis: an isoniazid therapeutic dose side effect

Lava Mohammad1,*, Leen Doya1,†, Razan Omran1, Alexander Ibrahim2,‡, Zuheir Alshehabi3 and Ali Ibrahim1

1Department of Pediatrics, Tishreen University Hospital, Lattakia, Syria, 2Department of Internal Medicine, Tishreen University Hospital, Lattakia, Syria, 3Department of Pathology, Tishreen University Hospital, Lattakia, Syria

*Correspondence address. Department of Pediatrics, Tishreen University Hospital, Lattakia, Syria. Tel: +00963991574342; E-mail: lavamohammad89@gmail.com

Abstract
Isoniazid (INH) is highly bactericidal against replicating tubercule bacilli and is involved in all antituberculous chemotherapeutic regimens. Several neurological adverse effects, following both therapeutic and overdose use of INH, have been reported in adults in the literature. Here, we present a case of a 5-year-old girl with intestinal Tuberculosis, who developed hemiclonic seizure as a side effect of INH therapeutic dose after 2 weeks of tuberculosis therapy.

INTRODUCTION
Isoniazid (INH) is the most widely used antituberculosis medication. The incidence of tuberculosis (TB) is ∼10% under the age of 10 [1]. According to the World Health Organization (WHO) 2017, TB in children represented 11% of total TB cases and the prevalence was 0.38 per 100 000 in the pediatric group in Syria [2]. INH, the wonder drug in the war against TB, was first discovered in 1951. It is bactericidal, easily administered, inexpensive and relatively nontoxic in children. Almost 10% of children develop transiently elevated alanine aminotransferase (ALT) levels while taking Isoniazid, but the clinical toxicity is exceedingly rare [3]. Major adverse effects include hepatitis and peripheral neurotoxicity that is uncommon at conventional doses [4].

CASE REPORT
A 5-year-old female patient was admitted to the Pediatric Department with a 1-month history of prolonged fever measured at 38.5–39°C at a rate of 4–5 times daily, partly controlled with antipyretic, associated with lack of appetite and weight loss of 4 kg. Although she was treated with various antibiotics, the fever continued to rise. In her medical history, there was diagnosed corrosive Esophagitis (caustic) and had several sessions of dilatation through the scope. The last one was about 8 months before admission. There was no family history of genetic disorders or contact with TB patients. The child underwent all the compulsory immunizations for her age.

On examination: Her body weight was 15 kg standard deviation (SD) (DS—1.8), the length was 100 cm (DS—1.3), temperature 38.3°C, oxygen saturation 98%, arterial blood pressure was 90/55 mm Hg, awake, breathing spontaneously, pale and there was bacillus Calmette Guerin (BCG) scar on her left shoulder. The abdomen was soft and the liver palpated 4 cm below the right costal margin. Other systems examinations were within normal limits.

Laboratory investigation reports were as in Table 1. The chest X-ray was normal. A Peripheral blood smear was as follows:

1Leen Doya, http://orcid.org/0000-0003-0814-5135
2Alexander Ibrahim, http://orcid.org/0000-0002-7395-9613
Received: September 15, 2020. Revised: October 26, 2020. Accepted: November 3, 2020
© The Author(s) 2021. Published by Oxford University Press.
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited.
For commercial re-use, please contact journals.permissions@oup.com
leukocytes increased in neutrophils, erythrocytes different sizes shapes, and lack of pigment and platelets increased in number. Echocardiography was normal. The abdominal ultrasound showed liver heterogeneous (13–14) cm, spleen relatively large, increased thickness in the intestinal fold at the end of the ileum, many of the lymph nodes around aorta and its branches were detected, the largest is 2-cm diameter. Neck ultrasound showed a single lymph node submandibular region measured 10 mm, and several nodes along the right carotid path, the largest one measured 22 mm. Bone marrow puncture was normal. Tuberculin skin test (TST) was positive (10 mm) diameter after 72 h (Fig. 1). Contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis showed the enlargement lymph nodes in the abdomen and pelvis around the abdominal aorta and in the iliac fossa, with an increase in the thickness of the colon wall and the end of the terminal ileum. In a colonoscopy, there was a disturbing mucosa, diffuse abrasions, swollen follicular formations and absence of vascular pattern found in Sigmoid and terminal ileum, with loss of normal morphology and severely ulcerative formulations in Cecum and Bohan valve (Fig. 2).

The pathology of several biopsies from colons showed an inflammatory infiltrate of lymphocytes without follicular formations (Fig. 3). The cecum biopsies showed the presence of granulomatous formations with epidermal cells with several giant cells of the Langhans type (Fig. 4). The Differential Diagnosis includes Tuberculosis and Crohn’s disease. The Ziehl Neelsen Stain (ZN) for bacillus was negative. We did not do the Culture because it was not available in our hospital. Antinuclear antibody, antineutrophil cytoplasmic antibodies, and TB polymerase chain reaction were negative. Anti-tubercular therapy was started with a regimen containing isoniazid, rifampicin, ethambutol and pyrazinamide for 2 months followed by isoniazid and rifampicin for 4 months. Vitamins B supplements were added to provide (1 mg/kg) vitamin B6. After 14 days of starting treatment of tuberculosis, the patient had hemiclonic seizure continued for 3 min. Phenytoin 15 mg/kg loading dose then complete with 5 mg/kg with stable in the seizure. CSF analyses, EEG, a CT of the brain were normal. The electrocardiogram, liver function tests and electrolytes were normal. Arterial Blood Gas (ABC) test was normal. INH levels and B6 levels were not available. The dose of INH was 15 mg/kg daily and this was not an overdose. The Seizure was a side effect of INH therapy after ruling out all other possible causes of seizure. After about 3 weeks of treatment initiation, the child was in good general condition, remarkable clinical improvement, and weight gain of about 700 g. The girl was discharged with instructions to follow the treatment of Anti-tubercular therapy and vitamins. We followed-up the patient for a year after the therapy and repeated the gastrointestinal endoscopy which was normal. The patient is healthy and does not have any symptoms of the disease now.

**DISCUSSION**

Abdominal tuberculosis (ATB) is a rare disease that can be challenging in diagnosis. ATB may be associated with abdominal pain (93%), episodes of intestinal obstruction (73%), fever (64%), and lack of appetite (52%), weight loss (47%) and diarrhea.
In our case, ESR elevation, positive TST, the enlargement lymph nodes in CT, besides the biopsies which revealed granulomatous lesions, diagnosis of ATB. We started antituberculous therapy, although PCR was negative.

INH is a first-line agent in the treatment of tuberculosis and is also used in preventive therapy. Its neurological side effects, including peripheral neuritis, dizziness and insomnia. Most reported INH-induced seizures occurred as a result of an overdose in suicide attempts or wrong taken by children \[4\]. Minns et al. \[8\] reported a case of a 10-month-old male infant was presented after being found with his father's INH.

The acute ingestion of INH at a dose above 30 mg/kg typically causes seizures, and INH ingestion of more than 80 mg/kg can rapidly cause death. Central nervous system effects occur due to vitamin B6 deficiency. The occurrence of seizures at conventional doses has rarely been reported. This report called by Tsunouchi et al. \[4\] in an 86-year-old woman who had convulsive seizures that occurred in association with the administration of a short-term therapeutic dose of INH. Puri et al. \[9\] also reported a case of a 65-year-old male who developed isoniazid induced seizures after the first therapeutic dose.

Three factors are influencing the risk of INH induced neuropathy. The first is the dose of INH used. The incidence of peripheral neuropathy is dose-related, with a large dose resulting in a high rate of adverse effects. The second factor is the patient's nutritional status. Money reported that the incidence of peripheral neuropathy is increased in malnourished patients. The third factor is the INH acetylation rate. Patients who acetylate INH slowly are at an increased risk of developing neuropathy \[4\].

In the case of INH toxicity, pyridoxine should be administered in a dose equivalent to the suspected amount of isoniazid ingested. If the amount of INH ingested is unknown, 5 g of pyridoxine should be given intravenously \[9\].

To date, our case has been the first case reported in the literature of seizures caused by INH in a child in a therapeutic INH. CSF analyses, EEG, a CT scan of the brain were normal. That denied meningitis to be the cause of the seizure. Our patient did not have any medical history of seizures. All other possible causes of seizures were ruled out by thorough clinical examination and relevant investigations.

Similar reaction can be expected in the future and patient should be monitored for the similar toxic effects during treatment.

**CONFLICT OF INTEREST STATEMENT**

All of the authors declare that they have no competing interests.

**FUNDING**

No funding was obtained for this study.

**ETHICS APPROVAL AND CONSENT TO PARTICIPATE**

This case report did not require review by the Ethics Committee Tishreen university hospital, Lattakia, Syria.

**CONSENT FOR PUBLICATION**

Written informed consent was obtained from the patient’s parents for publication of this Case report and any accompanying
images. A copy of the written consent is available for review by the Editor.

AUTHORS’ CONTRIBUTIONS
All authors have read and approved the manuscript.

AVAILABILITY OF DATA AND MATERIAL
All data generated or analyzed during this study are included in this published article.

REFERENCES
1. Lin YS, Huang YC, Lin TY. Abdominal tuberculosis in children: a diagnostic challenge. J Microbiol Immunol Infect 2010;43:188–93. doi: 10.1016/S1684-1182(10)60030-8.
2. WHO. 2018. Syrian Arab Republic: Country Profiles. [Online]. http://www.who.int/gho/countries/syr/country_profiles/en/ (24 August 2018, date last accessed).
3. Murray JF, Schraufnagel DE, Hopewell PC. Treatment of Tuberculosis A Historical Perspective: ATS Discoveries Series. AnnalsATS 2015;12. doi: 10.1513/AnnalsATS.201509-632PS.
4. Tsubouchi K, Ikematsu Y, Hashisako M, Harada E, Miyagi H, Fujisawa N. Convulsive seizures with a therapeutic dose of isoniazid. Intern Med 2014;53:239–42. doi: 10.2169/internalmedicine.53.1303.
5. Rathi P, Gambhire P. Abdominal tuberculosis. J Assoc Phys India 2016;64:38–47.
6. Makharia GK, Srivastava S, Das P, Goswami P, Singh U, Tripathi M, et al. Clinical, endoscopic, and histological differences between crohn’s disease and intesinal tuberculosis. Am J Gastroenterol 2010;105:642–51.
7. Sharma SK, Ryan H, Khaparde S, Sachdeva KS, Singh AD, Mohan A, et al. Index-TB guidelines: guidelines on extrapulmonary tuberculosis for India. Indian J Med Res 2017;145:445.
8. Minns AB, Ghafouri N, Clark RF. Isoniazid-induced status epilepticus in a pediatric patient after inadequate pyridoxine therapy. Pediatr Emerg Care 2010;26:380–1. doi: 10.1097/PEC.0b013e3181db24b6.
9. Puri MM, Kumar L, Vishwakarma PD, Behera D. Seizures with single therapeutic dose of isoniazid. Indian J Tuberc 2012;59:100–2.