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What is the Cause of Seizure: Isoniazid Poisoning or Epidural Hematoma? A Case Report

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ABSTRACT

Introduction: Isoniazid (INH) is the primary drug that is widely used in the treatment of tuberculosis. Because of the decrease in the incidence of tuberculosis, the usage of INH and its associated intoxications have decreased with time. In this case, we present a patient who was admitted to the emergency department (ED) with seizure attack, wherein it could not be determined whether the cause of the seizure was INH poisoning or epidural hematoma.

Case Report: A 26-year-old woman was brought to the emergency department because of self-poisoning with an over-dosage of INH. On arrival at the ED, she had a seizure. Arterial blood gas analysis revealed lactic acidosis and hyperglycemia. At the same time, she had a head trauma, and brain computed tomography demonstrated epidural hematoma; thus, 18 mg/kg phenytoin was initiated for seizure prophylaxis. Intravenous pyridoxine treatment was planned for intoxication of INH; however, the treatment was not available because of the absence of this drug in our local region.

Conclusion: As in our case, if the patient is concurrently diagnosed with epidural hematoma in addition to INH poisoning, it can be difficult to discriminate the cause of seizure. Although lactic acidosis, hyperglycemia, and seizure were defined as a classical triad for INH poisoning, this triad can be observed in many types of seizures.

Keywords: Isoniazid, seizure, epidural hematoma, pyridoxine

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Introduction

Isoniazid (INH) is the primary drug that is widely used in the treatment of tuberculosis. INH is a hydrazide derivative of isonicotinic acid and the primary drug for the prophylaxis and treatment of both active and latent tuberculosis. Although its bactericidal activity is unclear, it is considered to inhibit the synthesis of mycolic acid, a component of the cell wall of *Mycobacterium tuberculosis*. Furthermore, it is inhibits pyridoxal phosphate-dependent enzyme glutamic acid decarboxylase and decreases gamma aminobutyric acid (GABA), which is one of the most important inhibitory neurotransmitters in the central nervous system (1). Because of its inhibitory mechanism of the enzyme pyridoxine phosphokinase, it converts pyridoxine to pyridoxal-5'-phosphate. This is the activated form of pyridoxine and is a cofactor for glutamic acid decarboxylase and GABA transaminase. Both of these enzymes are important in the synthesis of GABA. INH metabolites bind to the inactive pyridoxal-5'-phosphate and decrease the GABA levels, thus reducing the seizure threshold by blocking the primary inhibitor mechanism of the central nervous system (2). Toxicity associated with INH is less frequent along with decreased incidence of tuberculosis and usage of INH. However, the use of INH can cause serious complications, such as seizures, respiratory failure, coma, and death. In this case, we presented a patient who was admitted to the emergency department (ED) with seizure, wherein it could not be determined whether INH poisoning or epidural hematoma was the cause.

Case Report

A 26-year-old female patient was brought to the ED for trying to commit suicide with excessive intake (unknown dose) of INH, and she had nausea, vomiting, and dizziness. In addition, it was learned that she fell down the stairs before admission. The patient's dizziness may have been signs or symptoms because of head trauma after falling. On arrival to the ED, she had generalized tonic–clonic seizures. The patient was admitted to the critical care room, oxygen was provided by mask, and treated with an

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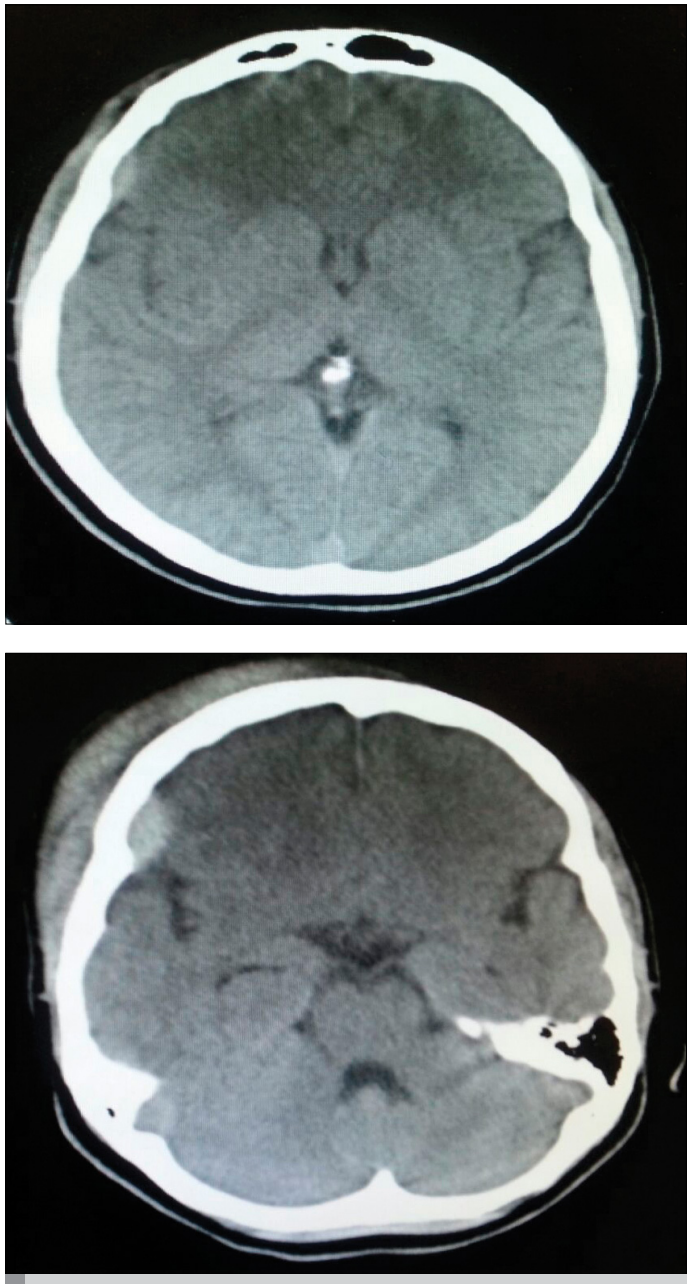

FIG. 1. a, b. Computed tomography image at the admission (a), computed tomography image at the 8th hour of admission (b)

intravenous administration of 10 mg diazepam to control the seizures. The patient's vital signs were: pulse, 123 beats/min; rhythmic blood pressure, 100/60 mmHg; respiratory rate, 14 breaths/min; and oxygen saturation, 96%. The Glasgow Coma Scale (GCS) score was 11, and in the electrocardiogram, sinus tachycardia was detected. On physical examination, there was 10×10 cm-sized cephalic hematoma in the right frontoparietal region. Cranial computed tomography scan of the patient was taken, and it revealed an approximately 1-cm epidural hematoma on the same side as the lesion area (Figure 1). Arterial blood gas analysis revealed that pH was 7.01, lactate was 8.9 mmol/L, and bicarbonate was 15.1 mmol/L. Laboratory studies of renal and liver function tests and electrolytes were within normal limits except sodium levels were 151 mmol, blood glucose were 229 mg/dL, and white blood cells were 15.3×103 /µL. Approximately 45 min after the seizure, the patient's consciousness and GCS were improved. In a detailed history, the patient declared she had taken 7.5 g INH approximately an hour ago for suicide. Approximately 1 g/kg oral doses of activated charcoal were administered, following gastric lavage. Intravenous pyridoxine treatment was scheduled for the patient with INH intoxication; however, it could not be initiated because of the absence of the drug in our local region. Therefore, 18 mg/kg phenytoin was initiated for seizure prophylaxis.

We referred the patient to the neurosurgery department for epidural hematoma. Neurosurgery did not determine any pathology requiring acute intervention and suggested hospitalization for observation. Approximately 8 h after admission to the hospital, the patient's seizures regressed and metabolic acidosis, bicarbonate, and blood glucose levels improved to normal levels. Although a control cranial computed tomography scan of the patient was taken, revealing epidural hematoma that progressed to 2.5 cm, the patient's GCS remained stable. The patient was admitted to the neurosurgery department for observation. On the fourth day after admission to the ED, she was discharged.

Discussion

Isoniazid intoxication is a rare condition because of the decrease in its use. It is reported that in the literature, INH is used at the dosage of 10 mg/kg/day for tuberculosis treatment, acute taken of 20 mg/kg and above concerned toxicity, intakes over 30 mg/kg may lead to seizures, and over 80 mg/kg can cause death. In our case, the patient had taken a large amount of 7.5 grams INH that is severely toxic.

Clinical signs of toxic intake begin within 30 min to 2 h. The main common side effects are nausea, vomiting, rash, fever, ataxia, slurred speech, visual disturbances, dizziness, stupor, peripheral neuritis, hypotension, tachyarrhythmia, bradycardia, tachypnea, and hyporeflexia. The most common laboratory findings are metabolic acidosis because of lactic acidosis, hyperglycemia, leukocytosis, and abnormal liver functions. The classical triads of high dosage INH poisoning are recurrent seizures, lactic acidosis, and coma (3). The causes of lactic acidosis are production of lactic acid during seizure activity and INH's interference with nicotine adenine dinucleotide, which is cofactor in the reaction that converts lactate back to pyruvate (4). Life-threatening symptoms are recurrent seizures, respiratory failure, renal failure, and coma, particularly at high doses of INH administration (5). Our subject had initial symptoms, such as nausea, vomiting, and dizziness, and she also had generalized tonic–clonic seizures. Seizures can be associated with intoxication; however, epidural hematoma after a trauma will be one of the etiological factors. With respect to the size of the hematoma, clinical findings that occurred are in the range from mild headache to confusion and coma. Epidural hematoma is classically presented by transient loss of consciousness followed by an alert or lucid interval and later by progressively decreased level of consciousness. In the presence of both etiological factors, it is difficult to determine the diagnosis.

To manage INH poisoning, there are three important methods. The first method is general supportive care for toxicology that includes gastric washout, active charcoal, and intravenous fluid resuscitation. The second method is management of life-threating symptoms, such as support airway, breathing, and circulation. The third method is treatment

of seizures. Previous animal studies have revealed that classical anticonvulsant agents, such as phenytoin, phenobarbital, or diazepam, could not treat INH-induced seizures (6). The seizures are considered to not respond to classical anticonvulsant treatment because of the GABA inhibition mechanism. To increase GABA levels in the central nervous system, the seizures should be treated with pyridoxine. The administered pyridoxine treatment must be equal to the amount of administered INH (gram-per-gram replacement). If the amount of INH is unknown, 5 grams of pyridoxine should be slowly infused at the rate of 1 g/min. This treatment stops seizures activity, reduces metabolic acidosis, and recovers consciousness (7).

Moreover, benzodiazepines enhance the effects of GABA at a dose of 5–10 mg, and diazepam could be added to the treatment as required. Severe acidosis (pH<7.1) requires treatment with sodium bicarbonate (1–3 mEq/kg) and close monitoring of arterial blood gas levels (6, 7). Hemodialysis should be considered in cases that do not respond to large doses of pyridoxine, anticonvulsants, or bicarbonate therapy (8).

Pyridoxine availability is relatively difficult. The results of a study implied that between one third and one half of the respondents would be ill-equipped to treat acute INH neurotoxicity (9). Most of the EDs are unprepared for the treatment of pyridoxine in INH intoxication. However, in a letter to editor, Zell–Kanter reported that a physician can administer oral pyridoxine tablets when intravenous form is unavailable (10). These pyridoxine tablets are absorbed within 20 min after administration.

In our case, we could not determine whether INH poisoning or epidural hematoma was the cause of the seizures. At the same time, because both of the diagnoses present as a cause of the seizure, there is no certain way to discriminate the etiology of the seizure. Despite the classical triad, which has been described for INH intoxication, this triad can be observed in seizures with various causes. Although the general seizure management procedures are similar, both of these causes must be differently treated. In our case, first, we provided support care and tried to control the seizure with diazepam. After we diagnosed the epidural hematoma, we decided to initiate phenytoin therapy. As we learned from the history, we decided to administer pyridoxine for INH poisoning, which is one of the possible cause of seizure; however, we could not find pyridoxine in our local region. The patient's seizures stop despite not receiving pyridoxine treatment.

Conclusion

In the ED, severe INH intoxication can be observed in patients with self-poisoning despite the decreased in INH usage. In addition, severe INH intoxication can result in seizures. As in our case, if the patient is concurrently diagnosed with epidural hematoma in addition to INH poisoning, it can be difficult to distinguish the cause of seizures. Regardless of etiological causes of seizures in patients admitted to the ED, it should be kept in mind that cranial tomography scan for head trauma should be performed to rule out brain injury. Although lactic acidosis, hyperglycemia, and seizures were defined as a classical triad for INH poisoning, this triad can be observed in many types of seizures.

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