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Case report

Secret Underlying Unexplained Abdominal Pain, Neurological Symptoms and Intermittent Hypertension: Acute Intermittent Porphyria

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Abstract

A 21-year-old female patient with abdominal pain, vomiting and constipation was admitted to the hospital with the possible diagnosis of diabetic ketoacidosis. Due to increased abdominal pain and constipation the patient underwent a surgery with the diagnosis of ileus. However, no pathological findings were found in the abdominal organs apart from serous fluid in the abdominal cavity. The patient became hypertensive, tachycardic and had an episode of seizures postoperatively. Neurological manifestations with unexplained abdominal pain indicated a diagnosis of acute intermittent porphyria (AIP). Acute intermittent porphyria diagnosis is based on elevated urinary δ-aminolevulinic acid (ALA) and porphobilinogen (PBG) levels as well as hydroxymethylbilane synthase (HMBS) IVS13-2 A>G heterozygous mutation. Familial Mediterranean Fever (FMF) gene mutations were not confirmed. Porphyria should be considered in the differential diagnosis of patients with recurrent abdominal pain, neurological symptoms and lack of FMF gene polymorphism.

Introduction

Porphyrias are a group of diseases caused by deficiency in the activity of enzymes related to heme biosynthesis [1]. The clinical manifestations of the disease are related to the accumulation of heme intermediates such as δ-aminolevulinic acid (ALA) and porphobilinogen (PBG) in various tissues [1]. Porphyria can be classified as cutaneous or hepatic [2]. Acute intermittent porphyria (AIP) represents the most common form of acute hepatic porphyria that depends on porphobilinogen deaminase deficiency and is manifested with increased urinary excretion of ALA and PBG [3,4,5]. Clinical signs usually appear after puberty and are more frequent in women [1]. Different stimuli such as hormonal factors, stress, prolonged fasting, infections, alcohol, porphyrinogenic drugs and reduced caloric intake may cause acute attacks. During attacks, abdominal pain, constipation, vomiting, hypertension, tachycardia, fever and various peripheral and central nervous system symptoms may be seen [4,5]. Hyponatremia due to inappropriate antidiuretic hormone secretion represents the most common electrolyte disorder in AIP.

Case

A 21-year-old female patient with a history of type 1 diabetes mellitus for nine years was admitted to the Emergency Department of the hospital complaining of vomiting, abdominal pain and constipation. The patient was treated with an intensive insulin regimen using aspart and glargine insulin. Upon further questioning, the patient stated that she had started cabbage and unbalanced diet (poor in carbohydrates and rich in proteins) one week prior to her admission in the hospital. She said that she was on regular insulin during this period. On physical examination blood pressure was 110/70 mm/Hg, heart rate 110 beats/minute and temperature 36.4ºC. The results of the laboratory tests in the emergency department are shown in Table 1.

The ultrasound scan of the abdomen showed no abnormalities and the patient was transferred to the Department of Internal Medicine with the possible diagnosis of diabetic ketoacidosis. Oral intake was interrupted and the patient was treated with intravenous insulin and saline infusion for 24 hours. Insulin infusion was stopped after ketones become negative in urine samples and intensive insulin therapy was restarted. As there were persistent complaints of abdominal pain and constipation for approximately 4 days during her hospitalization, the surgeons were called and the patient was transferred to the Department of Surgery. After a computed tomography (CT) scan of abdomen, the patient was operated with the diagnosis of ileus. However, apart from serous fluid collection in the abdominal cavity, no abnormal findings were observed. At the same time

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Table 1: Laboratory findings

Variables	Results	Reference values
Hemoglobin	10.8 gr/dl	12.2-16.2
Hematocrit	32.8 %	37.7-47.9
Mean Corpuscular Volume (MCV)	74.5 fL	80.0-97.0
Platelets	269 x10^3/uL	140-400
White blood cells	5.4 x10^3/uL	4.2-10.6
Neutrophil	2.8 x10^3/uL	2.0-6.9
Glucose	429 mg/dl	74-106
Urea	13 mg/dl	17-43
Creatinine	0.9 mg/dl	0.60-1.10
Aspartate Aminotransferase (AST)	68 U/L	0-35
Alanine Aminotransferase (ALT)	59 U/L	0-35
Lactate Dehydrogenase (LDH)	206 U/L	0-247
Albumin	3.3 g/dl	3.6-5.2
Sodium	128 mmol/L	136-146
Potassium	3.03 mmol/L	3.5-5.1
C-Reactive Protein (CRP)	0.434 mg/dl	0.000-0.800
Erythrocyte Sedimentation Rate (ESR)	8 mm/hour	0-20
Antinuclear antibody (ANA)	1/160 Nuclear stippling + 1/80 homogeneous	
Anti-Smooth-Muscle Antibody (ASMA)	Negative	
Antimitochondrial antibody (AMA)	Negative	
Glutamic acid decarboxylase (GAD) Antibody	7.93 IU/ml	>10 positive
Cortisol	17.19 µg/dL	6.2-.19.4
Toxoplasma gondii Antibodies, IgG	10.5 (positive)IU/mL	<7.2 Neg >8.8 Poz
Rubella IGG (the antibody)	152 (positive) IU/ml	< 9 Neg >11 Poz
IGG antibody to CMV)	99.4 (positive)IU/ml	< 0.4 Neg >0.6 Poz
Hepatitis B Surface Antigen	0.2 (negative) S/CO	
Hepatitis B Surface Antibody	> 1000.00 (positive) mIU/mL	
HIV Antibody	0.11 (negative)S/CO	
Hepatitis C virus (HCV) antibody	0.41 (negative)S/CO	
Aminolevulinic acid (ALA)	146 µmol/L	0-8 µmol/L
Porphobilinogen (PBG)	273 µmol/L	0-34 µmol/L

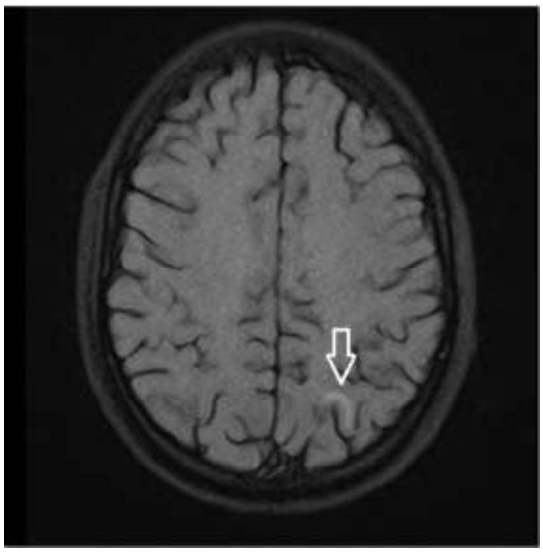

Fig. 1. Increased signal intensity in the occipital lobe as indicated by an arrow on the MRI image

gynecologists were also called, but again no gynecological abnormalities were found. During the first postoperative week, abdominal and back pains were repeated with increased intensity. The patient became hypertensive (160/100 mm/Hg) and tachycardic (150 pulse/ minute) on the 7th postoperative day and she developed tonicoclonic seizures that lasted for 3 minutes. A similar episode repeated twice. The patient was transferred to Intensive Care Unit because of deterioration of vital signs. Electroencephalography (EEG) showed paroxysmal abnormalities in the anterior cerebral hemisphere and magnetic resonance imaging (MRI) detected an increased signal intensity in the occipital lobe compatible with postictal edema (Figure 1). The laboratory results are shown in Table 1. Porphyria was considered in the differential diagnosis due to unexplained abdominal pain and neurological symptoms. ALA and PBG levels were measured in the urine. Urine ALA and PBG levels were found to be 146 µmol/L (reference values: 0-8 µmol/L) and 273 µmol/L (reference values: 0-34 µmol/L), respectively. Acute intermittent porphyria was diagnosed in the light of these results. AIP gene mutation were studied and hydroxymethylbilane synthase (HMBS) IVS13-2 A>G heterozygous mutation was found. Familial Mediterranean Fever (FMF) gene mutations were also studied but were not confirmed. Patients' symptoms regressed and vital signs were back to normal after administration of analgesics, beta blockers, insulin, intravenous dextrose and isotonic NaCl. Gabapentin was given in order to control seizures. After monitoring in the Intensive Care Unit she was transfe-

rred to the Department of Internal Medicine. Hyponatremia was considered secondary to SIADH, and sodium levels increased to normal with fluid restriction. Gabapentin was prescribed at a dose of 300 mg 2x1 daily. She was discharged with proper diet and instructions to avoid long-term fasting and porphyrinogenic drugs.

Discussion

AIP is a rare autosomal dominant metabolic disorder characterized by a deficiency of the enzyme PBG deaminase [6]. Its prevalence is 2-3 cases per 100000 persons per year [7].

Although the disease shows an autosomal dominant inheritance, genetic penetrance is low [8]. The most common presenting symptom of AIP is abdominal pain lasting from hours to days. Due to the characteristics of recurrent attacks of abdominal pain in acute intermittent porphyria, Familial Mediterranean Fever (FMF) should be considered in the differential diagnosis. FMF may be presenting with attacks of fever, abdominal pain, serositis and arthritis which are common manifestations in the Mediterranean Area, including our country. Furthermore, AIP should be considered in the differential diagnosis of patients with recurrent abdominal pain and with a negative FMF gene polymorphism. Patients with AIP might have symptoms that mimic acute abdomen which could lead to surgical intervention. In the case of suspected porphyria, after exclusion of possible causes of acute abdomen, urinary ALA and PBG levels should be measured [5]. Abdominal pain in patients with diabetic ketoacidosis is a common finding. In case of diabetic ketoacidosis, it is difficult to diagnose acute intermittent porphyria. On the other hand, ileus can be seen in patients with porphyria and ileus can cause abdominal pain. Porphyria should be considered in patients with unexplained abdominal pain or other characteristic symptoms. No clear association was defined between diabetes mellitus and AIP. One study suggests that there is a beneficial effect of diabetes on AIP [9]. There are no data indicating increased frequency of porphyria in type 1 diabetes. According to American Porphyria Foundation, some foods such as charcoal-broiled meats, cabbage, and Brussels sprouts contain chemical substances which can up-regulate hepatic ALA synthase 1. The amounts of such foods that could induce hepatic ALA synthase 1 have not been carefully studied [10]. AIP patients should be fed a balanced diet with moderate carbohydrate, protein and fat consumption and should avoid long periods of fasting or excessive diet. Dextrose infusion is recommended during an acute attack. Due to the diagnosis of type 1 diabetes, dextrose and insulin were administered at same time. Yang *et al*. have studied the types of HMBS mutations in Chinese patients with AIP and identified twenty-five HMBS mutations [11]. We found HMBS IVS13-2 A>G heterozygous mutation in our patient. AIP may affect the autonomic, peripheral and central nervous systems. Neurological symptoms of acute porphyrias include severe pain, paresis, peripheral neuropathy, muscle weakness, difficulty swallowing, other bulbar signs, confusion, delirium and seizures [12]. Posterior reversible encephalopathy syndrome (PRES) is a rare clinico-neuro-radiological entity and a rare presenting feature of AIP. PRES has distinct clinical and neuroimaging features and is characterized by sudden onset of headache, seizures, altered mental status and visual disturbances. MRI studies typically show edema involving bilateral white matter of posterior cerebral regions, especially the parieto-occipital lobes, and sometimes the frontal and temporal lobes. Other encephalic structures may also be involved [13]. Although AIP is associated with encephalopathy and epilepsy, few cases have been reported in the literature.

Conclusion

Our patient had severe muscle pain in legs and lumbar region. She developed tonicoclonic seizures that lasted for 3 minutes and repeated twice. These findings were attributed to neurological involvement of AIP and similar supportive therapy applied to AIP attacks was used. AIP should be kept in mind in the approach of patients with epileptic encephalopathy in the clinical practice. The choice of the antiepileptic drug is an important feature in preventing triggering of attacks as well as in treatment itself. In patients who have AIP and are admitted in emergency room with acute attack, the treatment should begin immediately. They should be treated with a high carbohydrate intake (at least 300 g/day), narcotic analgesics for the pain, beta blockers for tachycardia, intravenous hydration and electrolyte replacement if necessary. Fluid restriction should be considered in case of SIADH in patients with AIP. The most important part of treatment is to avoid any stimulus that can trigger an attack [14]. Porphyria needs to be considered in the differential diagnosis of patients with neurological symptoms, unexplained abdominal pain and intermittent hypertension.

Conflict of interest statement. None declared.

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