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Acute intermittent porphyria after right hemi-colectomy☆

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ABSTRACT

INTRODUCTION: Acute intermittent porphyria is a rare autosomal dominant metabolic disease. It is caused by a genetic mutation that results in deficiency of porphobilinogen deaminase enzyme, the third enzyme in heme biosynthesis. Acute intermittent porphyria precipitated by surgery is very rare.

CASE PRESENTATION: We present a 24 year-old woman who developed acute intermittent porphyria five days after right hemi-colectomy. Her presentation included neuro-visceral and psychiatric manifestations, and severe hyponatremia. She received critical care symptomatic management including mechanical ventilation. The diagnosis was based on a positive urine test for porphobilinogen and confirmed by the presence of a heterozygous mutation in the hydroxyrmethylbilane synthase (*HMBS*) gene (c.760delC p Leu254).

DISCUSSION: Acute intermittent porphyria is the most common and life threatining type of acute porphyrias. It is more common in women and usually presents after puberty with acute abdominal pain and diverse neuro-psychiatric manifestations that can be confused with several surgical and medical diseases. Acute intermittent porphyria after surgery is most likely due to postoperative pain and low-calorie intake. Once suspected, prompt ICU management including high calorie intake are necessary to avoid serious complications and mortality before starting definitive treatment with hematin.

CONCLUSION: Acute intermittent porphyria should be suspected in any patient, particularly young women, who develop diverse neuro-visceral and psychiatric manifestations and hyponatremia after surgery.

1. Introduction

Porphyrias are inherited inborn errors of metabolism of heme biosynthesis. They are classified into eight types based on the clinical presentation (acute/cutaneous) and site of metabolic defect (hepatic/erythropeitic) [1,2].

Acute porphyrias include acute intermittent porphyria (AIP), variegate porphyria, hereditary corpoporhyria and delta-aminolevulinic acid (ALA) dehydratase deficiency porphyria [1–3].

Acute intermittent porphyria, an autosomal dominant hepatic type, is due to partial deficiency of porhobilinogen (PBG) deaminase, the third enzyme in heme biosynthesis. This deficiency leads to increased production and excretion of porphyrin precursors, PBG and ALA [1,2]. The prevalence of the genetic defect responsible for AIP is as high as one case per 500 persons. Because of the partial deficiency of PBG deaminase (50% of the normal level) only 10–20% of the gene carriers develop AIP after exposure to risk factors (triggers) and 80–90% remain biochemically and clinically normal during their lives [1–3].

Acute intermittent porphyria is the most common and life threatening type of acute porphyrias. It is more common in women and usually presents itself after puberty with diverse visceral, neurological and psychiatric manifestations that can be confused with several surgical and medical diseases [3–7].

In Saudi Arabia, there is no data on the incidence of AIP and only one case was reported concerning a young woman with AIP mimicking acute cholecystitis [8].

Acute intermittent porphyria after surgery is very rare with only few case reports in the literature [9–13]. We present what we believe is the first case of AIP after right hemi-colectomy.

2. Case presentation

This work has been reported in line with the SCARE criteria [14].

A 24 year-old- single female patient was admitted because of right lower abdominal pain and distension for 2 weeks. The pain was colicky, episodic, with no precipitating factors and only

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relieved after bowel motion. She had no constitutional symptoms of chronic illness. She was not on any medications and her social history was unremarkable. Her menstrual cycle was regular and she was menstruating one day after admission. Physical examination revealed a thin patient in mild pain distress with normal vital signs. Her abdomen was soft and lax with normal bowel sounds. Routine laboratory tests including CBC and renal and liver function tests were normal. Serum transaminases remained normal during her hospital stay. Aspartate aminotransferase (AST, SGOT) range was 18–33 U/L (normal range: 15–37 U/L). Alanine aminotransferase (ALT, SGPT) range was 25–51 U/L (normal range: 14–63 U/L). On admission, level of serum sodium (Na) was normal: 138 mEq/L (normal range 135–145 mEq/L) and remained normal (range: 135–139 mEq/L) until the 5th postoperative day (see below). Plain abdominal X-ray and abdominal computed tomography (CT) showed a distended cecum located in the pelvis with fecal impaction; the rest of the viscera were unremarkable. These findings were consistent with mobile cecum syndrome. The patient was scheduled for laparoscopy and possible laparotomy. The only abnormality during laparoscopy was that the cecum and ascending colon were not attached to posterior abdominal wall. The procedure was converted to laparotomy. Right hemi-colectomy was performed. She was kept on epidural analgesia, intravenous (IV) fluids and nil by mouth for four days and had a smooth post-operative course. After surgery, she received intravenous (IV) 5% dextrose/0.9% NaC) three liters/day (her weight was 48 kg). In addition, her pain was controlled by epidural analgesia of lidocaine and fentanyl. The histology revealed normal colon. On the 5th postoperative day, oral intake was resumed and epidural analgesia was discontinued. Eight hours later, she had a sudden deterioration of consciousness level and became unresponsive with a Glasgow Coma Scale of 7/15. Her pupils were dilated and had a sluggish reaction to light. The patient was immediately intubated, mechanically ventilated, resuscitated, and admitted to the intensive care unit (ICU). Blood work up revealed severe hyponatremia; serum Na: 107 mEq/l with normal renal and liver function tests. Our differential diagnoses for the severe hyponatremia included drug intoxicity, encephalitis, and salt losing nephropathy. Consultations to neurology and psychiatry were made and they advised brain CT scan and magnetic resonance imaging (MRI), and cerebrospinal fluid analysis. These tests and septic work-up were normal. She was extubated two days later. At this stage, she started to complain of acute abdominal pain and developed altered mental status, personality changes, visual and auditory hallucinations with euphoric and aggression episodes despite correction of serum Na.

The presence of abdominal pain, neurological and psychiatric symptoms and unexplained severe hyponatremia raised the suspicion of AIP. The diagnosis of AIP was based on the presence of high PBG in the urine (test was done at another center). At no time, her urine was dark. In retrospect, the family history showed that two of her cousins (from mother side) had AIP. The patient condition improved markedly after proper pain control and high carbohydrate intake. We referred her to a higher center where she was found to have a heterozygous mutation in the hydroxyrmethylbilane synthase (*HMBS*) gene (c.760delC *p* Leu254). There, she received premenstrual regime of IV hematin (heme arginate) 4 mg/Kg body weight/day for three days. She had four recurrent milder attacks in the form of abdominal and back pain and confusion and was treated with similar regime of hematin. Thereafter, she was kept on once monthly prophylactic IV hematin 4 mg/Kg body weight/day for three days. Now, one and a half years after discharge from our service, she is doing fine and on no hematin treatment.

3. Discussion

Although it is difficult to prove retrospectively, it is possible that our patient's initial symptoms were the start of a mild attack of AIP, which unrecognized progressed after surgery to a full acute attack. However, we believe that based on the imaging and operative findings the initial diagnosis of our patient was mobile cecum syndrome [15]. We initially performed laparoscopy which confirmed the diagnosis of mobile cecum syndrome. Because of the surgical team preference, the procedure was converted to laparotomy. We did right hemi-colectomy rather than cecopexy because of the good general condition of the patient and to prevent recurrence. Based on our routine practice, the patient was kept NPO for four days. She had a smooth postoperative course. Most likely, her attack of AIP was precipitated by a combination of (1) hormonal changes during menstruation, (2) epidural analgesia of lidocaine and fentanyl, (3) low-calorie intake during the postoperative period (510 Kcal/day) and (4) surgical site pain after cessation of epidural analgesia [1,11]. Medline search revealed only five cases of AIP after surgery (Table 1) [9–13]. Other triggers that increase the demand for heme and hence induce AIP include porphyrinogenic drugs, infections, smoking, alcohol intake, fasting, psychological stress, and hormonal changes associated with menstruation and ovulation [1–3].

Similar to our case, the classical patient of AIP is a woman in her third decade of life [3,5–8]. Abdominal pain is the most common severe presentation of AIP being present in 85%-95% of patients. It is usually attributed to autonomic neuropathy. However, Lithner believes that protracted vascular spasm with resultant intestinal ischemia is the cause of abdominal pain in AIP [5]. In AIP the severity of abdominal pain is often disproportionate to findings on abdominal examination. In addition, fever and leukocytosis are usually absent [3]. Other manifestations include pain in extremities, head or neck (50–70%) muscle weakness (42–68%), paraesthesia, seizure (20%), anxiety, depression, and psychosis. Tachycardia and hypertension are the most common cardiovascular manifestations being present in 28–85% and 36–55% of cases, respectively [1,2]. These neuro-visceral and psychiatric manifestations are most likely due to involvement of the autonomic, peripheral and central nervous system secondary to elevated PBG and ALA [1–3]. Similar to others, family history of AIP in our patient was positive [3,5,11]. But at times, patients give no family history of AIP [1,3].

From the surgical point of view, AIP can be mistaken for other causes of abdominal pain such as acute appendicitis, acute cholecystitis, intestinal obstruction, gastric perforation, bowel ischemia, and ovarian torsion [3,5–8]. Other differential diagnoses of AIP include psychosis, Guillian Barré syndrome, and encephalitis [7,11,13]. Hence, a high index of suspicion is needed to diagnose AIP.

Routine laboratory tests including WBC are usually normal but some patients with AIP have elevated hepatic transaminases [4,8,10]. Severe hyponatremia can complicate AIP and similar to our case requires ICU management. The exact pathophysiology of hyponatremia in AIP is not fully understood. However, hyponatremia is most likely due to vomiting, administration of hypotonic IV fluids and syndrome of inappropriate antidiuretic hormone secretion (SIADH) [2,3]. Usually the urine turns dark when exposed to sunlight [3,8,10]. As seen in our case, this finding is sometimes absent [4]. Abdominal and brain CT scan and MRI, gastro-intestinal endoscopy, CSF analysis, electromyography and nerve conduction studies are usually normal or non-specific [1,3,4,6,7,10,13]. The diagnosis of AIP is based on elevated levels of urinary PBG (as in our patient) and 5-aminolevulinic acid (ALA) and confirmed by DNA study for hydroxymethylbilane synthase (HMBS) gene mutations [1–3,8].