

LATE ACUTE INTERMITTENT PORPHYRIA ATTACK IN A PATIENT WITH TYPE 2 DIABETES

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received: March 12, 2015 accepted: May 17, 2015

available online: June 15, 2015

Abstract

Background. Acute intermittent porphyria (AIP) is a hereditary metabolic aberration resulting from a partial defect in the activity of the enzyme porphobilinogen deaminase (PBDG) during the course of haeme synthesis. Diabetic metabolism may attenuate the episodes of porphyria related symptoms. **Case report.** Our subject (male; age 75) was hospitalized one week after onset of diffuse abdominal pain and constipation and overt type 2 diabetes mellitus (DM). The patient's long history of alcohol intake with acute alcohol consumption 12 days before admission, in the presence of abdominal pain with spectacular remission after oral administration of 5% glucose solution, accompanied by a 2.5 fold increase of urinary porphobilinogen with normal values for porphyrins and urinary lead, and normal full blood count establishes the diagnosis of AIP. **Conclusion** We describe a case of AIP probably triggered by acute alcohol consumption, with neurovisceral dominant clinical picture mimicking an acute abdomen. Late disease occurrence as first acute episode at older age accompanied by overt type 2 DM, suggests a latent type of AIP in our patient. The appropriate recognition of latent AIP cases in proband's offspring prevents unnecessary blind surgery when repeated episodes of unexplained abdominal pain occur.

key words: acute intermittent porphyria, diabetes, type 2

Introduction

Acute intermittent porphyria (AIP) is an autosomal hereditary metabolic aberration resulting from a partial defect in the activity of the enzyme porphobilinogen deaminase (PBDG) during the course of haeme synthesis [1]. Clinically pattern is characterized by recurrent attacks of abdominal pain and neuropsychiatric symptoms. The pathogenesis is based on accumulation of porphyrin precursors, prior to the third enzymatic step, which is responsible for the clinical expression of AIP. Acute attacks of

porphyria are most commonly precipitated by events that decrease haem concentrations, thus increasing the activity of aminolevulinic acid (ALA) synthetase and stimulating the production of porphyrinogens. Acute exacerbations may be precipitated by a number of triggers, including drugs, physiological hormonal fluctuations, alcohol intake, fasting, dehydration, stress and infection [1]. Metabolic disturbances encountered in diabetes may retard, prevent, decrease the severity and frequency or even lead to the complete disappearance of episodes of porphyria related symptoms [2]. We report a

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case of AIP occurring in an old patient with overt type 2 diabetes mellitus (DM).

Case report

A 75-year-old man has presented to the hospital with diffuse abdominal pain and constipation. The patient had been in his usual state of health until approximately one week before admission when recurrent abdominal pain and constipation (one formed stool at four days) appeared. His appetite was normal and the pain wasn't directly associated with food ingestion. He also reported sleep-onset insomnia and uncontrolled chronic hyperglycemia. He did not report fever, nausea or vomiting.

The patient's symptoms were nonspecific. The differential diagnosis of abdominal pain includes a large spectrum of clinical conditions from benign and self-limited to life-threatening diseases. The common diseases that must be taken into account are gastrointestinal diseases including peptic ulcer disease, appendicitis, diverticular disease or pancreatic-bile disorders like biliary colic, acute gallbladder disease and pancreatitis. Mesenteric ischemia and infarction are important clinical conditions to consider in elderly patients presenting with acute diffuse abdominal pain. Severe, acute diffuse abdominal pain can be caused by either partial or complete bowel obstruction or metabolic disease such as diabetic ketoacidosis. Other potential cause of abdominal pain to consider is referred pain from inferior wall acute myocardial infarction, aortic aneurism dissection or nephrolithiasis. The duration of the symptoms and the non-continuous character of the pain made the acute abdomen diagnosis unlikely for this patient.

The patient's medical history included type 2 DM and hypertension. The diagnosis of DM had been made 3 years earlier with a fasting glucose level of 170 mg per deciliter, without any symptoms. The patient's regular medications included: Gliclazide 60 mg twice a day,

Enalapril 10 mg twice a day, Indapamide 1.5 mg once a day, Amlodipine 5 mg once a day, Acetylsalicylic acid 75 mg once a day. The patient had no surgical history. He is retired and lives alone. He had no history of smoking or toxic environmental exposure but had a long history of alcohol intake. Furthermore, he reported high (unspecified) ingestion of alcohol 12 days before admission. His family history was positive for DM (one son has type 2 diabetes).

Abdominal pain seems not to be in the context of a diabetic ketoacidosis as this condition mostly appears in type 1 DM, although it can occur also in patients with type 2 DM, under certain circumstances. Usually, in type 2 DM insulin production is present and even minimal amounts of insulin are sufficient to suppress ketogenesis, even more for this patient with a relatively recent onset of diabetes mellitus. On the other hand, diabetes mellitus is associated with increased incidence of *Helicobacter pylori* infection related gastritis and with gastroparesis. Another history clue that could explain the patient's clinical picture is alcohol abuse that is a common cause of abdominal disorders including gastritis and pancreatitis. The patient's reported chronic alcohol abuse suggests also the possibility that alcohol withdrawal may be contributing to the patient's symptoms. Type 2 diabetes mellitus and hypertension are two clinical conditions associated with atherosclerosis, which can be the cause of mesenteric ischemia. Typically, mesenteric infarction presents with the acute and severe onset of diffuse and persistent abdominal pain, while chronic mesenteric ischemia presents with abdominal pain after eating. The absence of this typically clinical presentation renders this diagnosis less probable.

On physical examination, the patient was anxious, non-febrile, blood pressure was 160/90 mmHg, the heart rate was regular at 84 beats per

minute, the respiratory rate 16 breaths/min. Respiratory and cardiac examinations were normal. Abdominal examination revealed diffuse tenderness at palpation without guarding or rebound tenderness, no organomegaly or abdominal masses, and normal bowel sounds. Murphy's sign was absent. Neurologic examination showed paresthesias and decreased sensation to light touch in both legs. The patient weighs 86 kilograms, has a height of 1.73 meters and a BMI of 28.73 kg/m². Otherwise the examination was normal. Digital rectal examination was normal with no fecal occult blood and no masses.

The patient's physical findings were not suggestive for an acute life-threatening condition. There are no general signs, no abdominal distention and no signs of peritoneal irritation. The absence of Murphy's sign and the diffuse character of the pain make biliary disease unlikely. Even though myocardial ischemia can manifest with abdominal discomfort, the absence of other associated symptoms argue against this disorder. In the presence of neurologic damage (distal symmetric sensory neuropathy), diabetic neuropathy may be considered as a cause of abdominal pain.

The aim of initial emergency evaluation on admission was to rule-out a potentially life-threatening cause of abdominal pain. Therefore abdominal ultrasound scan, electrocardiography, biochemical laboratory tests including cardiac markers for acute myocardial infarction, was performed. Electrocardiogram showed a normal sinus rhythm and left ventricular hypertrophy without acute ischemic changes. The cardiac enzyme levels CK-MB and LDH were within normal range. The abdominal ultrasound exam revealed a heterogeneous liver echo-texture, gallbladder with sludge, multiple left kidney small stones with dilated superior calyx and no fluid in the peritoneal cavity. The results of laboratory tests included a white-cell count of

8700/mm³ with a normal differential count, the hemoglobin 15.10 g/dl with a normal mean corpuscular volume, the hematocrit 43.90%, and the platelet count of 230.000/mm³. Serum electrolytes levels and acid-base parameters were within normal limits. The creatinine concentration was 1.58 mg/dl, and may probably reflect a mild chronic renal disease in an old patient with uncontrolled blood pressure and overt type 2 diabetes. Acute renal injury seems less probable as no other acute kidney damage and/or acute fluid retention was documented. Liver-function tests, serum amylase and lactic dehydrogenase levels were within normal limits. Glucose value on admission, according to finger-stick testing after an overnight fast, was 334 mg/dl, while glycated hemoglobin (HbA1c) value was 9.26%.

Acute myocardial infarction was excluded in the absence of electrocardiographic changes and elevated cardiac enzyme levels. The normal white-cell count does not support the diagnosis of an inflammatory process such as appendicitis and in combination with a normal serum lactic dehydrogenase level argues against bowel obstruction or mesenteric ischemia. Abdominal pain is unlikely to be explained by the biliary sludge or renal micro-lithiasis. Although lipase serum concentration wasn't measured, normal amylase level was an argument against pancreatitis. Even if the blood glucose level on admission was high, there were no other parameters to support diagnosis of diabetic ketoacidosis. Increased HbA1c value supports chronic hyperglycemia. The ultrasound liver appearance, in the absence of signs of hepatic cytolysis, indicates hepatic steatosis, probably toxic, nutritional and dysmetabolic.

In the first 24 hours from admission the patient received the following treatment: oral hydration; diet counseling with 270 grams of carbohydrates and salt restriction; correction of hyperglycemia with regular insulin; symptomatic

treatment of visceral pain, antacids as ulcer-like symptomatic treatment and pro-kinetics to improve gastrointestinal motility; antihypertensive therapy. Surgical examination found no specific indication. During this time, the patient continued to report intermittent abdominal pain, which occurred especially in the evening, with relative remission on antispastic and antisecretory medications.

The patient required further evaluation. The chest radiography was normal, with no evidence of acute lung/pleural injury or free air under the diaphragm. The upper gastrointestinal endoscopy revealed biliary reflux gastritis. Native abdominal computer scan revealed no pathological abnormalities. Helicobacter pylori antibodies blood test was negative. The creatinine level decreased when compared to the value at admission reaching 1.46 mg per deciliter. Therefore, an acute renal injury was excluded, and the mild kidney dysfunction needs subsequent follow-up on a regular basis. The glomerular filtration rate estimated by the MDRD4 formula was 59.3 ml/min/1.73 m². Biochemical analysis of urine revealed urinary albumin excretion rate of 60.86 mg/dl. First documentation of a modest proteinuria in a patient with uncontrolled DM and high blood pressure was interpreted as a marker of diffuse endothelial damage. Serum levels of amylase, lactic dehydrogenase, transaminases, total and direct bilirubin, and triglycerides were within normal range. Fundoscopic examination of the eye showed a normal posterior pole.

The physical findings correlated with laboratory and imagistic tests at this stage provided no support for an obvious abdominal pathology, which could explain the clinical picture. At this point, we are left to discuss the less common possible causes of neurovisceral pain such as mixed neuropathy (diabetic and alcoholic neuropathy), alcohol withdrawal

syndrome, heavy metal poisoning (especially lead), acute intermittent porphyria and psychogenic pain.

Accordingly, the following diagnostic and therapeutic approach was chosen: oral administration of 5% glucose solution during painful abdominal attacks with spectacular remission of pain; elimination of potentially porphyrinogenic drugs including sulfonylurea agent; glycemic long term control by initiating subcutaneously basal insulin regimen using a long acting insulin analogue; quantization of urinary lead; measurement of porphobilinogen, uroporphyrins, coproporphyrins excretion in twenty-four hours urine specimen, collected under special conditions (container kept cold and protected from the light). Depending on the amount of porphyrins and the intensity of the exposure, urine of AIP sufferers may turn dark purple when exposed to ultraviolet light and air after 24 hours of exposure. The colorless porphobilinogen is changed to the dark colored porphobilin due to oxygen exposure [1].

Lead concentration in urine (atomic mass spectroscopy, Floreasca Emergency Hospital) was normal (8.16 mg/L). Urinary excretion of porphyrin precursors (spectrophotometric chromatography, Synevo Laboratories) revealed the following pattern: porphobilinogen (photometry, Synevo Laboratories) 5.2 ng per liter (normal <2 ng per liter); uroporphyrins 12.79 µg per day (normal 15-50 µg per day); coproporphyrins 50.84 µg per day (normal 35-150 µg per day); total porphyrins 63.64 µg per day (normal < 220 µg per day).

Based on the latest findings, we established the diagnosis of acute intermittent porphyria (AIP). Our supposition was supported by the clinical presentation with recurrent abdominal pain, constipation and insomnia; glucose cessation effect on abdominal pain; patient's history of long-term alcohol use with an acute

alcohol intake before hospital admission; and a normal full blood count [1].

The clinical course during hospitalization was impacted by recurrent episodes of abdominal pain ceased by glucose intake and significantly decreased relapses over last 72 h prior to hospital discharge. While hospitalized, the patient presented four stools of normal consistency after evacuatory enema. The other critical curves (skin temperature, urine output, blood pressure, pulse, respiration) evolved favorably.

Discussion

We described a case of acute intermittent porphyria probably triggered by acute alcohol consumption, with neurovisceral dominant clinical picture mimicking acute abdomen, in the absence of motor neuropathy.

Porphyrins consist of four pyrrole rings derived from the precursors glycine and succinyl-CoA, which are converted to δ -aminolaevulinic acid (δ -ALA) in a reaction catalysed by the limiting enzyme δ -ALA synthase [3]. The enzyme has two mitochondrial isoforms named as ALA-N (non-erythroid) and ALA-E (erythroid), with different regulation. While ALA-N is under negative feedback by haeme, upregulated by drugs and chemicals, and has no known inherited deficiency, ALA-E is not affected by haeme and drugs, and has an inherited deficiency, which is responsible for X-linked sideroblastic anemia. Two molecules of δ -ALA condense to form a pyrrole ring. The reactions start in mitochondria, passes through cytoplasm, and generates haeme back into mitochondria. Hemoglobin is generated into cytoplasm where haeme is combined to globin chains. Porphyrins can be classified into uroporphyrins, coproporphyrins or protoporphyrins depending on the structure of the side-chain. They are termed type I if the structure is symmetrical and type III if it is asymmetrical [3].

Porphyrias are classified as hepatic or erythroid depending on which main tissue the haeme precursors accumulate in, and as acute or chronic depending on the major clinical manifestations [1]. The enzyme deficiency responsible for each disorder is partial, at least in acute forms of the disease (approximately 50% of normal). Conversely, the remaining enzyme activity is usually sufficient for haeme homeostasis. However, porphyrias exhibit a nonspecific and polymorphous clinical picture, with a broad spectrum of signs mimicking neuropsychiatric, dermatologic, gastrointestinal or endocrinologic diseases that lead to various diagnostic traps in clinical judgement [4]. Moreover, different types of porphyrias may associate [5]. The combined prevalence of acute porphyrias, including AIP, is about 5 cases per 100,000 persons [1]. In spite of heterogeneity, the major clinical manifestations of acute porphyrias are neurological, while the most striking biochemical findings are the common overproduction of ALA and porphobilinogen [1]. While porphyrins (tetrapyrroles) are also increased, their measurement is of little value for initial diagnosis because they are also increased (in urine, feces, erythrocytes, or plasma) in other porphyrias and many other medical conditions.

An accurate and rapid diagnostic of an acute attack of porphyria may results at least in less neurologic damage and pain discomfort. Therefore, a three-step approach (Table 1) has to be considered for the early diagnosis of acute porphyria [1].

We considered this approach for our case, documenting a more than 2.5 increase of urinary porphobilinogen. In spite of lack of ALA measurement, the normal levels of porphyrins in urine specimen established the diagnosis of AIP. The gold standard for the diagnosis of the abnormal haeme synthesis would consist in direct assaying for PBGD activity within the

tissue involved, i.e. the erythrocytes [6]. The immediate application would be the undoubtedly detection of both the patient and the patient's offspring carriers of the disease.

Table 1. Early diagnosis of acute porphyria (modified after [1]).

1. Consider in all adults with unexplained symptoms seen in acute porphyrias; certain clinical features are suggestive: women of reproductive age; abdominal pain; muscle weakness; hyponatremia; and dark or reddish urine.
2. Establish diagnosis promptly by testing for increased porphobilinogen in a single-void urine. If porphobilinogen is increased, begin treatment immediately.
3. To establish the type of acute porphyria, save the same urine sample for measurement of ALA, porphobilinogen, and porphyrin levels, and measure plasma porphyrin levels, fecal porphyrin levels, and erythrocyte porphobilinogen deaminase levels.

Late disease occurrence with first acute episode at an older age, suggests a latent type of AIP in our patient. Moreover, the overt diabetes mellitus is an additional argument for this scenario [2]. This assumption seems valid in both the patient and his relatives, especially when the fact that one of his sons has diabetes is considered. Animal studies on rats demonstrated that the basal levels of the key ALA synthase enzymes involved in haeme synthesis, were decreased after diabetes induction and that the haeme catabolism via microsomal haeme oxygenase progressively decreases during the course of diabetes [7]. Urinary porphobilinogen level is substantially increased (20 to 200 mg/L) in patients with acute attacks of AIP [1]. The relative modest increase in urinary porphobilinogen observed in our case may also reflect a decreased severity of haeme metabolism alteration in presence of the diabetic milieu.

In absence of a specific treatment for AIP, clinical evolution and prognosis of this patient is influenced by immediate and long term complications, due to exposure to triggers, especially alcohol [1].

The immediate risk when AIP attack onsets are electrolytes metabolism disturbances causing

cardiac sudden dysrhythmia or encephalopathy. Long-term complications related to AIP are mainly represented by hepatocellular cancer, worsening of hypertension and renal injury [1,8,9]. The hypothesis explaining the hepatocellular carcinogenesis is based on both the accumulation of porphyrin precursors, which could lead to intrinsic production of mutagenic substances through auto-oxidation of ALA, and the reduction of free haeme pool, thus compromising the antioxidant defense [9].

By avoiding precipitating factors, e.g. drugs and alcohol, further acute attacks may be prevented. A high-carbohydrate diet should be maintained. Carbohydrates intake specifically blocks ALA-N. However, the exact mechanisms by which carbohydrates modulate the components of porphyrins and haeme synthesis are highly complex and have not yet been fully understood [2].

Conclusion

This case report highlights that in front of a patient suffering from repeated episodes of unexplained abdominal pain, diagnosis of the rare metabolic causes, i.e. AIP, should always be considered. The appropriate recognition of AIP cases (i.e. the proband and proband's offspring) is of great importance as it can easily lead to diagnostic inference usually entailing unnecessary blind surgery with subsequent acute stress induction and symptoms relapses.

Conflict of interest: The authors declare there is no conflict of interest for this study.

Funding: This work received financial support through the project entitled "CERO – Career profile: Romanian Researcher", grant number POSDRU/159/1.5/S/135760, cofinanced by the European Social Fund for Sectoral Operational Program Human Resources Development 2007-2013.

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