

Acute Intermittent Porphyria – A Rare Autosomal Dominant Disorder Presenting as Acute Abdominal Pain

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Abstract

Abdominal pain is a common symptom with a broad spectrum of etiologies and is sometimes a challenge to approach. We report a rare case of acute intermittent porphyria presenting as acute abdominal pain. Acute intermittent porphyria should be considered in patients with unexplained abdominal pain, especially linked to a suspected family history or accompanied by other neurovisceral symptoms, such as vomiting, constipation, and muscle weakness. An accurate diagnosis is important in order to initiate appropriate therapy and avoid progressive neurologic damage. (J Intern Med Taiwan 2012; 23: 449-452)

Key Words: Acute intermittent porphyria, Porphobilinogen, Hemin

Introduction

The porphyrias are a group of rare hereditary metabolic disorders, each subtype arising from a catalytic dysfunction of one of the eight enzymes along the porphyrin-heme biosynthetic pathway. One subtype, acute intermittent porphyria (AIP), is inherited in an autosomal dominant fashion and caused by mutations in the hydroxymethylbilane synthase (HMBS) gene, which results in a catalytic deficiency of HMBS, the third enzyme in heme biosynthesis¹. While the prevalence of a mutant AIP gene may be as high as 1 per 500 in Finland, penetrance is incomplete and the prevalence of symptomatic disease is only 1–2 per 100,000².

Symptoms of AIP are due to effects on the visceral, peripheral, autonomic, and central nervous systems and are highly variable and nonspecific. Abdominal pain is the most common symptom of AIP, occurring in 85-95% of patients with acute attacks³. Symptoms usually occur intermittently and sometimes are life-threatening with a significant mortality of up to 5% that require rapid therapeutic intervention to prevent complications such as paralysis, respiratory failure, coma, and death¹.

Case Presentation

A 36-year-old woman with a history of fatty liver was brought to our emergency department because of intermittent lower abdominal pain for

3 days. Nausea, vomiting, and dark urine were also noted. Her consciousness was alert without neurological deficits. Vital signs were stable, except for tachycardia with a heart rate at 114/min. Lower abdominal tenderness was found. Laboratory data, including complete blood count, urinalysis, serum creatinine, alanine aminotransaminase, amylase, glucose, sodium, and potassium, were within normal range. Abdominal radiography showed accumulation of a large amount of feces and a mild increase of bowel gas compared to its normal degree (Figure 1). A tentative diagnosis of constipation was made, and an enema was performed.

However, severe abdominal pain persisted. Abdominal ultrasonography did not reveal significant findings, except for an underlying fatty liver (Figure 2). A gynecologist was consulted but there was no abnormal finding. Abdominal computed tomography did not show any obvious abnormalities either (Figure 3).

Due to the patient's mentioning about a



Figure 1. Large volume of feces and mildly increased bowel gas as revealed by abdominal radiography.

suspected family history of porphyria, including her father and her diseased paternal aunt, though who had never been diagnosed, urine porphyrin levels were tested and the result was positive. The patient was admitted to the hospital under the impression of acute porphyria, and intravenous glucose was given. Because of poor response, intravenous administration of hemin 250mg daily was started on the second day and lasted for four days. The abdominal pain subsided after the treatment and the patient was discharged.

Because of planning for pregnancy, the patient visited the outpatient department of the Division of Obstetrics & Gynecology for genetic diagnosis. The DNA test showed a heterozygous mutation in the exon 13 of the HMBS gene (Figure 4). In Figure 4, the reported c.848G>A (p.W283X) indicates a DNA mutation from G to A resulting in a switch from Tryptophan (W) to stop codon (X). Her family, including her father, mother, a brother and

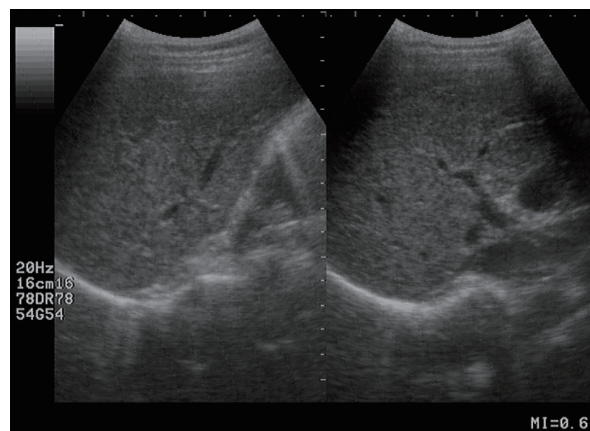


Figure 2. Heterogeneous echo texture of the liver as revealed by abdominal ultrasonography.



Figure 3. Excessive fluid with air bubbles in the small bowel loops as revealed by abdominal CT.

a sister, also received DNA testing. Her father and sister were found to be heterozygous carriers of the HMBS mutations (Figure 5).

Discussion

Symptoms in acute porphyria begin most often in the second to the fourth decade of life and are more common in women than in men¹. Severe neuropathic abdominal pain, the most frequent symptom, is diffuse rather than localized and is often accompanied by nausea, vomiting,

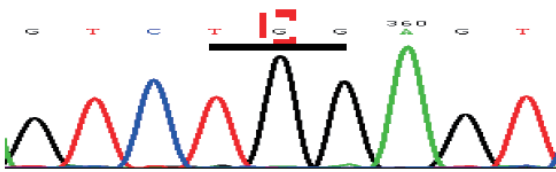
distention, constipation, and sometimes diarrhea³. Dark or reddish urine is often an early sign due to a high concentration of porphobilin, a brownish auto-oxidation product of colorless porphobilinogen and reddish porphyrin^{2,3}.

Urinary porphobilinogen level is substantially increased in patients with acute attacks of AIP and is recommended as the initial rapid test. Treatment can be initiated with a positive result of the test. The diagnosis is confirmed by a group of second-line tests which include measurements of erythrocyte porphobilinogen deaminase activity as well as urine, plasma, and fecal porphyrin levels measured in samples collected before any treatment¹⁻³.

Because intravenous hemin addresses the underlying pathophysiology by repressing hepatic delta aminolevulinic acid (ALA) synthase activity and decreases the overproduction of ALA and porphobilinogen, hemin therapy is recommended for acute porphyria attacks. Intravenous glucose loading which has some repressive effect on hepatic ALA synthase is less effective than hemin and is suggested only for early treatment of mild attacks. Precipitating factors, such as porphyrinogenic drugs (e.g., diclofenac, metoclopramide, progesteron, and those that induce hepatic cytochrome P450), alcohol, smoking, starvation, and infection should be avoided or prevented¹⁻³.

Approximately 80% of carriers with a gene mutation for acute intermittent porphyria remain asymptomatic, and others may have only one or a few acute attacks throughout their lives³. However, patients with AIP are at risk for developing chronic renal failure and hepatocellular carcinoma, so regular follow-up is recommended^{3,4}. Elevation in serum transaminase is also associated with AIP⁵. The HMBS mutation should be identified by DNA testing to enable accurate identification of other gene carriers in a family¹⁻³.

Wild-type:



Patient: heterozygous c.848G>A (p.W283X)

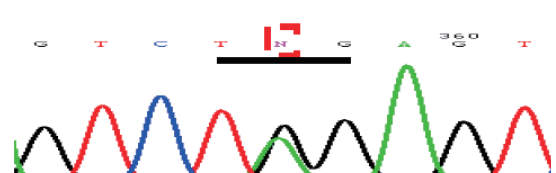


Figure 4. Results of the DNA screening for mutations in the coding sequences and exon-intron boundaries of the HMBS gene by polymerase chain reaction and direct sequencing.

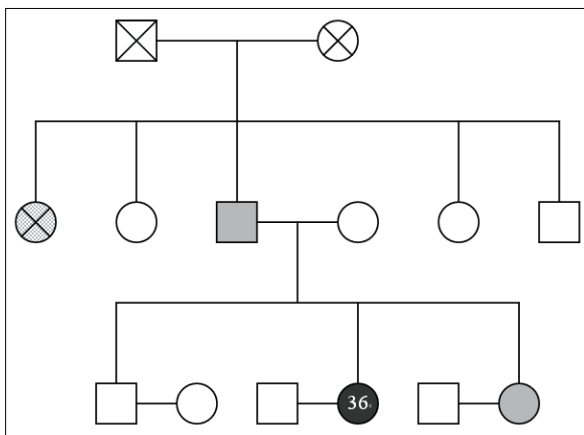


Figure 5. The 36-year-old female patient, with both her father and sister, are heterozygous carriers of the HMBS mutations. The patient's paternal aunt, who expired with severe abdominal pain and psychosis, was suspected to have undiagnosed acute porphyria episodes.

References

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急性間歇性紫質症： 一個以急性腹痛表現的罕見體染色體顯性遺傳疾病 之病例報告

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摘要

急性腹痛是臨床上常見的一種症狀，但很多疾病都可能以急性腹痛表現，確診有時相當困難。一位36歲的女性急性腹痛，初步無法找到病因，後來問及紫質症 (porphyria) 的家族病史，檢查尿中的紫質 (porphyrin) 果然呈現陽性，之後給予靜脈注射葡萄糖、血晶素 (hemin)，症狀逐漸改善。對於無法解釋的腹痛，急性間歇性紫質症 (acute intermittent porphyria) 必須列入鑑別診斷，特別是有此家族史、或伴隨其他神經內臟 (neurovisceral) 症狀，例如：嘔吐、便秘、肌肉無力等。確定診斷才能及時給予適當的治療，以防止進一步的神經學傷害。