

Case Report*Open Access, Volume 3***Acute hepatic porphyria attack following
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Abstract

Acute Intermittent Porphyria, (AIP) is a rare disease caused by Hydroxymethylbilane Synthase (HMBS) deficiency. It is characterized by acute neurovisceral attacks, in which excessive heme production is induced following exposure to a trigger. One of the suggested triggers is low carbohydrate intake. We report a 32-year-old female who suffered from severe abdominal pain, nausea and general weakness following a bariatric mini gastric bypass surgery. There was a positive family history of AIP, but the patient had a normal Porphobilinogen urine test as a child, therefore diagnosis was not made. During current symptoms, urinary porphobilinogen was highly increased and AIP was diagnosed. Treatment with IV dextrose and Heme Arginate alleviated the patient's symptoms. After discharge, Family genetic testing revealed a novel pathogenic mutation in the HMBS gene. Had genetic testing been performed earlier, diagnosis of AIP could have been established earlier. Early diagnosis may prevent attacks and reduce their severity. Since a bariatric surgery leads to low intake of carbohydrates, it might be an indirect trigger of an acute porphyria attack.

Keywords: porphyria; bariatric surgery; porphobilinogen.**Introduction**

Acute Intermittent Porphyria, (AIP) is a rare disease that belongs to the group of three autosomal dominant Acute Hepatic Porphyrias (AHP), caused by loss of function mutations in one of the genes involved in the heme biosynthesis pathway [1-3].

All three AHP–AIP, Variegate Porphyria (VP), and Hereditary Coproporphyria (HCP) are characterized by acute attacks, in which excessive heme production is induced following exposure to a trigger. As a result, heme precursors delta- Aminolevulinic

Acid (ALA) and Porphobilinogen (PBG) accumulate and are excreted in the urine [1-3]. The majority of acute attacks initially manifest as a combination of abdominal pain and mental symptoms (such as severe fatigue and inability to concentrate), with or without autonomic dysfunction [2,3]. Subsequently, abdominal pain may become worse, accompanied by nausea, vomiting, constipation, and signs of increased sympathetic activity (such as tachycardia and hypertension) [4]. Further exacerbation may follow with complete paralysis, respiratory failure, seizures [5], severe hyponatremia, and even death [6]. Many triggers of an AHP attack have been described, such

as drugs, alcohol consumption, infections, endogenous and exogenous hormones, and prolonged fasting [2].

Diagnosis of porphyria

It is important to emphasize that the diagnosis of acute porphyria should be considered in patients with severe abdominal pain when clinical evaluation has not revealed a cause.

Other features which should raise the level of suspicion include dark or reddish urine, hyponatremia, hypertension, tachycardia, vomiting and constipation [2,3]. While VP and HCP can usually be diagnosed biochemically during the latent phase (due to typical porphyrin accumulation characteristics), AIP may not be apparent. Therefore, current guidelines suggest testing for suspected porphyria during a symptomatic phase, where the diagnostic study of choice is the measurement of urinary ALA and PBG levels [7]. Advanced biochemical and genetic testing could further classify the type of porphyria; however, this classification does not influence acute treatment options [3]. Genetic screening of family members remains extremely important and allows prevention and rapid treatment which, can dramatically change the course of the disease [8].

Management of acute porphyria attacks

Cessation and avoidance of porphyrogenic drugs, treatment of infections with safe medications, and maintenance of adequate carbohydrate and energy intake are all essential first steps to treat AHP attacks [2,3]. In severe or refractory attacks, the treatment of choice remains intravenous heme [2,3].

Case report

A 32-year-old woman, with a history of hypothyroidism and obesity, was admitted to a referral hospital in Israel due to severe abdominal pain, nausea, vomiting, and general weakness. Two weeks earlier, a bariatric mini gastric bypass was performed in another hospital. Short post-operative follow-up was unremarkable, and the patient was discharged after two uneventful days. A few days thereafter, she started suffering from severe abdominal pain and nausea. An abdominal and pelvic Computed Tomography (CT) scan found no abnormal findings. Considering her persistent symptoms, an exploratory laparoscopy was performed one day prior to her current presentation and was unremarkable.

During her index admission, the patient reported poor oral intake, vomiting, and weight loss of 7 kilograms since her operation. Vital signs were normal, except for mild tachycardia, with a heart rate of 95/min. Physical examination revealed a normal healing surgical scar. Her abdomen was diffusely tender, with no signs of peritoneal irritation. While her blood counts were unremarkable, chemistry panels showed concurrent hyponatremia, hypokalemia, and hypomagnesemia. Kidney and most liver function tests were normal. Amylase, Gamma-Glutamyl Transpeptidase (GGT), and C-reactive protein were mildly elevated. The results of the main laboratory tests are shown in Table 1.

The patient was admitted to the surgical ward, and started on Intravenous (IV) fluids, Proton Pump Inhibitors (PPIs), and analgesics.

Table 1: Main laboratory tests.

Sodium [136 – 145 Millimole/liter]	131
Potassium [3.5 - 5.1 Millimole/liter]	2.8
Magnesium [0.7 – 1 Millimole/liter]	0.6
Phosphor [0.8 - 1.7 Millimole/liter]	0.9
Calcium [2.08 - 2.65 Millimole/Liter]	2.31
Creatinine [49 – 90 micromole/liter]	78
Albumin [32 – 48 gram/liter]	38
Alanine transaminase [10 – 49 Units/liter]	27
Aspartate transaminase [0-34 Units/liter]	34
Alkaline phosphatase [46 – 116 Units/liter]	74
Gamma-glutamyl transpeptidase [0 – 38 Units/liter]	51
Amylase [30-118 Units/liter]	322
Creatine phosphokinase, [Units/liter]	107
C- reactive Protein [0-0.5 milligram/deciliter]	0.95
White blood cell [4.05 - 11.84 10 ⁹ /liter]	8.6
Hemoglobin [12.4 - 16.1 gram%]	13.5
Platelets [203 – 445 10 ⁹ /liter]	218

Upper gastrointestinal fluoroscopy was preformed and was unremarkable.

On day 3 of hospitalization, the patient's father came to visit. Upon the patient's request, her operative status was not declared to him. Bearing in mind that his wife had suffered from similar symptoms many years ago and was accordingly diagnosed with Acute Intermittent Porphyria, the father decided to contact our Israeli porphyria center for consultation. After a case discussion between the porphyria specialists and the surgical staff, a safe drug list was provided, and a urine specimen was collected and sent for urinary delta Aminolevulinic Acid [ALA] and Porphobilinogen [PBG] testing. Results were available the next morning and were unequivocal for an Acute Hepatic Porphyria attack, as ALA and PBG levels were increased to 55.6 and 116 mg/gr creatinine respectively (normal values: up to 7.5 for ALA; up to 2.5 for PBG)

It is worth mentioning that porphyria-guided biochemical testing at the age of 10 was negative.

Following the diagnosis, treatment was started with dextrose therapy and Heme Arginate (Normosang). Due to a temporary national shortage of the drug, only two doses of 250 mg were supplied, however. Within a few days, remarkable clinical improvement ensued, and the patient was discharged. Ten days thereafter, her symptoms re-appeared, necessitating re-admission for receiving IV dextrose and two further doses of Heme Arginate. A higher caloric oral intake was advised as well. The patient gradually recovered and was later discharged. After discharge, family genetic testing was preformed and found a heterozygous change in intron 6 of the Hydroxymethylbilane Synthase (HMBS) gene; c.344+1G>C(het), g.118960471. While this mutation was not previously reported, it is classified as pathogenic in the Var Some database.

Discussion

In the present case, the patient suffered an acute porphyria attack following a mini bypass surgery. She had a positive family history of AIP, yet she had been only biochemically tested for porphyria during a latent phase, thus the disease passed undiagnosed until the current attack. It is important to point out that this disorder has reduced penetrance, estimated at around 1% in the general population and between 20 and 50% in families with an affected proband [9]. This suggests the role for other genetic and environmental factors in inducing the onset of symptoms [1,9]. Low carbohydrate intake might induce ALAS1 via Peroxisome proliferator-activated receptor Gamma Coactivator 1- α (PGC-1 α), a protein which directly induces transcription of ALAS1 [10]. Scarce previous reports suggested prolonged fasting to be a trigger of an attack in the setting of intercurrent illness, peri-surgical fasting, or a crash diet [11,12]. As bariatric surgery is a procedure that leads to low carbohydrate intake and weight loss, it might be an indirect trigger of an AHP in porphyria carriers. Two earlier reports described acute attacks of porphyria in VP and HCP patients following bariatric surgery [13,14]. In both cases, the diagnosis of porphyria was delayed and considered only after ruling out other possibilities. All typical symptoms appeared for the first time in our patient, as well as in the similar cases reported, only during this first attack. Our patient had a prolonged and resistant disease course, probably due to the distress of the bariatric surgery. However, had the family history been known to the patient, the diagnosis could have been established earlier, by examining the affected gene in AIP, HMBS, and perhaps the attack could have even been prevented [8,15]. It is worth mentioning that patients who continue to suffer recurrent attacks despite the best preventive measures are candidates for Givosiran treatment. The latter is a subcutaneously administered RNA interference therapeutic targeting hepatic ALAS1 Messenger RNA (mRNA), thereby preventing the accumulation of ALA and PBG. [15]

This case highlights some important messages; First, Bariatric surgery may be dangerous in AHP patients and should be weighed carefully before being performed. Second, a cluster of clinical and laboratory findings, including severe abdominal pain, vomiting, hyponatremia, and/or neurological symptoms following a bariatric surgery should raise suspicion of an acute porphyria attack. Third, during a suspected porphyria attack, a urine test for PBG is still the best way to assess the diagnosis of porphyria, while biochemical testing during a latent phase of AIP may not suffice. Until genetic testing is performed, asymptomatic family members of an AIP patient should be considered as potential latent patients, regarding all preventive measures. Last, the novel mutation c.344+1G>C in intron 6 of the HMBS gene is causative for AIP.

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