Acute Intermittent Porphyria – Diagnostic and Treatment Traps

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Acute intermittent porphyria (AIP) is a rare metabolic disease defined by mutations coding the deaminase enzyme of porphobilinogen (PBGD). Porphyrias are somewhat misdiagnosed as a consequence of light symptoms in patients. Acute forms of porphyria can be life-threatening, so a correct diagnosis and an accurate treatment are highly important. The authors presented the case of a 38-years-old patient admitted for persistent abdominal pain that previously presented two generalized convulsive seizures. The diagnosis of AIP was established by the raised concentration of urinary porphyrins. Despite treatment with carbohydrates and hemines, the clinical picture of the patient worsened, with tetraplegia and severe respiratory failure. The patient died seven weeks after the initial presentation of the disease.

Key words: acute intermittent porphyria (AIP), neurologic complications.

Porphyrins were named for the Greek root for “purple” (porphyria) [1][2]. The name porphyria is commonly credited to Schultz, who was a German medical student in 1874. B.J. Stokvis, MD, made the first clinical description of acute porphyria in 1889. In 1930, Hans Fischer, a Nobel laureate, described heme as the crypt that makes blood red and grass green. In 1937, Waldenström in Sweden published his findings on one specific type of porphyria, acute intermittent porphyria (AIP). By the 1960s, all known types of porphyria had been identified and environmental factors were shown to affect the disease course. Research in the 1980s and 1990s led to the identification of the molecular defects in each type of porphyria [3]. Currently, scientists have focused on gene therapy as a treatment for porphyria [2].

Porphyrias are a group of 8 inherited disorders of heme biosynthesis. A deficiency of any of the 8 enzymes in the biosynthetic pathway can lead to a variety of clinical symptoms. The disorders are classified as neurovisceral, cutaneous, or mixed, depending on the clinical manifestations [1][4][5].

Acute intermittent porphyria has been mistaken for so many diverse syndromes that, in the words of Watson “it well deserves the sobriquet of little simulator” [7] or “little imitator” by Waldenström [8][9].

Misdiagnosis is relatively common because the symptoms are vague. Acute attacks were the most feared manifestation, and are mainly a consequence of central, peripheral and autonomic nervous damage [10]. The most common signs and symptoms of AIP are abdominal pain (80%), constipation (50%), nausea and vomiting (50%), tachycardia (40%), hypertension (31%), urine discoloration (25%), fever (16%), seizures (10–16%), respiratory paralysis (9–14%) [2][11–13].

Many factors can precipitate acute attacks in patients with porphyria, including hormones, medications, nutritional status, tobacco use, infection, liver damage, surgery, and stress [15–20]. Numerous medications or “second hits” trigger or unmask symptoms [20]. The most common include sulfonamides, barbiturates, and ethanol [21]. Drugs may precipitate symptoms by inducing cytochrome P-450s and increasing the demand for heme synthesis [22]. Starvation and illness activate heme oxygenase, which depletes the hepatic heme pool leading to aminolevulinic acid synthase (ALAS) induction. Tobacco contains polycyclic aromatic hydrocarbons, which also induce cytochromes and increase heme synthesis [8].

However, acute forms of porphyria can be life-threatening, so accurate diagnosis and initiation of proper medical management is important [22].

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CASE PRESENTATION

History and initial evaluation

The patient, a 38-years-old woman, was hospitalized in the Department of Surgery of Colentina Clinical Hospital for diffuse severe abdominal pain; the diagnosis established was acute pancreatitis. The abdominal pain started two weeks before the admission, she attended emergency room consultation, but while she had menstruation, modifications of urine pigmentation could not be identified. Then she presented at home two generalized seizures.

The patient was a non-smoker, she was not an alcohol drinker or consumer of forbidden substances, she did not present a history of psychiatric disorders or skin sensitivity to sunlight and her family history was not significant.

At admission, the physical examination revealed paleness of the skin, cyanosis of the inferior limbs, spontaneous and palpatory sensitive abdomen, predominantly in the epigastric and right hypochondrial areas, hyperchromic urine (“pot-wine urine”), diminished deep tendon reflexes, bradylalia and bradypsychia.

At this moment, the paraclinic evaluation showed hypotension, hyperkalemia and raised hepatic cytolyse enzymes; 3 days later the patient presented with a severe electrolytical imbalance (Table I). The other biochemical markers were in normal ranges.

Symptomatic therapy was administered, but the persistent symptomatology imposed an interdisciplinary evaluation: psychiatric, that diagnosed an acute psychotic episode, neurological, that highlighted moderate decrease in muscular force upmost present at the proximal level of inferior limbs, global diminished deep tendon reflexes, bradylalia, bradypsychia, and hematological evaluation. Unexplained hypotension, the recurrence of abdominal pain, the acute psychotic episode and changes of pigmentation in urine raised the suspicion of AIP; an elevated urine porphyrin concentration confirmed the diagnosis (Table II).

Hydroelectrolytical infusions, thiamine and glucose infusions with a total intake of 400 grams of carbohydrates were administered.

Subsequent hospital course

The patient was transferred in the Department of Hematology, at that moment she presented with peripheral facial diplegia, predominant proximal teraplegia, all deep tendon reflexes were abolished, severe bradypyschia, bradylalia; the laboratory tests evidenced severe hyponatremia (103 mmol/L), severe hypokaliemia (1.4 mmol/L), hypochloremia (60 mmol/L), leukocytosis with neutrophilia.

Severe hydroelectrolytical disturbances and acute respiratory failure, secondary to respiratory muscles palsy imposed the transfer to the Intensive Care Unit and the orotracheal intubation with assisted mechanical ventilation.

The lack of improvement in symptomatology after the therapy with glucose infusions and the progressive course of motor deficit represented an indication for hematine therapy-4 mg/kgw/24 hrs, a total of 15 hematine doses were administered.

The persistence of fever was an indicator for spute examination that pointed an infection with Enterobacter which enforced antibiotic treatment allowed in AIP, depending on bacterial sensitivity (that was modified during hospitalization) and in permanent adjustment of doses function of creatinine clearance.

Also, the patient presented with major hemodynamic instability, with blood pressure variations from 60 to 220 mm Hg, that imposed inotropic-vasopressor support constantly and in raising doses, especially in the end stage.

Echography of the heart and of brachial veins designated the presence of pericardic fluid in medium quantity and permeable brachial veins.

The neuropsychologic examination (the measuring of motor and sensitive conduction velocities of peripheral nerves) and the neuroimagistic evaluation (cerebral MRI) could not be performed for logistic reasons and in the presence of severe respiratory failure that needed constant mechanical ventilation.

The clinical course was constantly worsening, the patient died secondary to toxico-septic shock with multiple organ and system failure (Table III).

<table>
<thead>
<tr>
<th>Table I</th>
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<tbody>
<tr>
<td>Biochemical changes in the first days of admission</td>
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<tr>
<td><strong>At admission</strong></td>
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<tr>
<td>Kalium (mmol/L)</td>
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<tr>
<td>Natrium (mmol/L)</td>
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<td>Chloride (mmol/L)</td>
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<td>ALT (IU/L)</td>
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<td>AST (IU/L)</td>
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</table>
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Table II
Biochemical changes of porphyrin in the first days of admission

<table>
<thead>
<tr>
<th>Urinary metabolites</th>
<th>Values at the diagnosis moment</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>0.066</td>
<td>In normal ranges</td>
</tr>
<tr>
<td>ALA/24 hrs</td>
<td>111</td>
<td>0–7 mg/24 hrs</td>
</tr>
<tr>
<td>Porphobilinogen/24 hrs</td>
<td>81</td>
<td>0–4 mg/hrs</td>
</tr>
<tr>
<td>Total porphyrins</td>
<td>4723</td>
<td>&lt;220 µg/24 hrs</td>
</tr>
<tr>
<td>Uroporphyrin</td>
<td>3319</td>
<td>15–50 µg/24 hrs</td>
</tr>
<tr>
<td>Coproporphyrin</td>
<td>1404</td>
<td>35–150 µg/24 hrs</td>
</tr>
<tr>
<td>Urinary volume/24 hrs</td>
<td>3100</td>
<td>1500–2500 mL/24 hrs</td>
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Table III
Biochemical parameters in the end stage

<table>
<thead>
<tr>
<th>Values in the end stage</th>
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<tr>
<td>Ionogram Kalium (mEq/L)</td>
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<tr>
<td>Natrium (mEq/L)</td>
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<tr>
<td>Chloride (mEq/L)</td>
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<tr>
<td>Liver function tests</td>
</tr>
<tr>
<td>Direct bilirubins (mg/dL)</td>
</tr>
<tr>
<td>Total bilirubins (mg/dL)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
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<tr>
<td>AST (U/L)</td>
</tr>
<tr>
<td>Renal tests</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
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<tr>
<td>Coagulation tests</td>
</tr>
<tr>
<td>APTTr</td>
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<tr>
<td>INR</td>
</tr>
<tr>
<td>Nonspecific inflammatory tests</td>
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<tr>
<td>Fibrinogen (mg/dL)</td>
</tr>
<tr>
<td>d-Dimers</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
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DISCUSSION

Pathogenesis of acute intermittent porphyria

AIP, also known as pyrroloporphyria, is the most common acute porphyria and is caused by deficiency of hepatic porphobilinogen (PBG) deaminase activity. Affected persons have a 50% reduction in PBG deaminase activity in their erythrocytes [23].

Porphyrins are intermediate products in the heme biosynthetic pathway. Heme is a necessary component of both cellular hemoproteins produced primarily in the bone marrow, which makes hemoglobin and, in the liver which makes the metabolizing enzymes, cytochrome P-450s. Of the 250 mg of heme synthesized per day, 200 mg is for hemoglobin. Normally, only 4 to 5 mg of the intermediates in the pathway accumulate, presumably owing to their toxic nature. Heme that is not used immediately in a protein complex, is metabolized to bile pigment [2][24].

The first step is the formation of δ-amino-levulinic acid (ALA) from glycine and succinyl coenzyme A. Subsequent steps involve the following:

1) synthesis of a substituted pyrrole compound, porphobilinogen; 2) condensation of 4 porphobilinogen molecules to yield porphyrinogen; 3) modification of the side chain and ring; and 4) introduction of iron to form heme. In most tissues, heme, the end product, is required to suppress further production of heme. If no heme is present to inhibit the pathway, production of heme continues unopposed. Any drug, chemical, or hormone that induces heme synthesis also produces an increase in heme precursors [2][8][22][24] [26–28].

Only protoporphyrin is used in heme synthesis. The other porphyrins have no physiologic function and must be excreted [12]: proto-and coproporphyrins in feces; uro- and coproporphyrins in the urine and plasma [25][29]. Their fluorescent properties account for the diagnostic appearance of urine in some patients.

Diagnosis of acute intermittent porphyria

Diagnosis of porphyrias is usually made by clinical history in association with increased amounts of porphyrins or porphyrin precursors in the urine, feces and blood [16][17][30–32].
Assays of urinary ALA and porphobilinogen (PBG) assist in this differential diagnosis. The urinary excretion of these porphyrin precursors is markedly increased during acute attacks and the urine may appear reddish brown because of the nonenzymatic formation of porphyrins and other pigments from PBG. Normal levels of ALA in particular, and of PBG, indicate that the patient is not suffering from an acute attack, but do not exclude an underlying porphyria. Markedly raised excretion of ALA and PBG, which improves following an infusion of the specific treatment heme arginate, confirms the diagnosis of acute porphyria. Intermediate values may cause some diagnostic difficulty, but a therapeutic trial of heme arginate usually proves of value. Differentiation of the four types of acute or mixed porphyria requires specialized biochemical analysis of plasma, red cells, urine and feces, usually undertaken at a specialized centre (Fig. 1) [2]. Rapid screening tests are useful in the initial evaluation. The Watson-Schwartz and Hoesch tests detect PBG in the urine by its reaction with Ehrlich’s reagent to produce a red color.

Figure 1. Algorithm for the laboratory workup of neurovisceral porphyrias.–normal; +elevated; ADP, δ-aminolevulinic acid dehydratase porphyria; AIP, acute intermittent porphyria; ALA, δ-aminolevulinic acid; HCP, hereditary coproporphyria; HPLC, high-performance liquid chromatography; PBG, porphobilinogen; VP, variegate porphyria [2].

Although the enzyme defects underlying the porphyrias have been identified, molecular genetics is not yet suitable for primary diagnostic purposes. Analysis of gene mutations is largely used for family studies, allowing pre-symptomatic diagnosis, when biochemical investigations are equivocal.

False-positive results can be seen in certain clinical situations [1][33]. Patients with hepatobiliary disease or lead toxicity may have elevated urine porphyrin levels. Factors such as a diet rich in meat or gastrointestinal bleeding can increase fecal protoporphyrins [2]. In iron deficiency anemia or lead toxicity, red blood cell porphyrins can be elevated; however, more than 90% are zinc protoporphyrins, which will not leak into the plasma [1]. Patients with chronic renal failure do not excrete porphyrins and can have pseudoporphyrin and elevated uroporphyrin levels in the urine [34]. Several diseases can masquerade as porphyria, such as intoxication (ethanol, chemicals-hexachlorobenzene, polyhalogenated biphenyls, dioxins, vinyl chloride, carbon tetrachloride, benzene, chloroform, lead, arsenic, mercury), liver disease, infectious disease (mononucleosis), hematologic disease aplastic anemia, thalassemia, leukemia, pernicious anemia, iron deficiency anemia), cancer (hepatocellular, metastatic, pancreatic), pregnancy, hereditary hyper-bilirubinemia, carbohydrate fasting, and hereditary tyrosinemia. It is important to differentiate between porphyrias and other more common diseases [17][22].

**Particularity of the case**

The patient presented previous to admission two generalized convulsive seizures that can be secondary to both toxic effects of ALA and PBG at the hypothalamic level (acting as direct neurotoxins) [12], and the syndrome of inappropriate secretion of antidiuretic hormone and consecutive hypotremia (identified at admission).

Abdominal pain, peripheral neuropathy, and changes in mental status are the classic triad of an acute attack [5][50], this triad raising also in our case the suspicion of AIP. Severe abdominal pain is the most commonly reported presenting symptom during acute attack [6][13][21][28][35][37][38]. A clinical presentation without abdominal pain is unusual in acute porphyria, and some authors suggest that initial screening tests should be limited to patients with this symptom [5][13][39][40].

Among patients with acute porphyria, 20–58% have neuropsychiatric symptoms during acute
exacerbations [5][20][38][41]. The neuropsychiatric symptoms (anxiety, depression) were present in our patient too, imposing psychiatric evaluation from admission; the diagnosis of acute psychotic episode was established. The pathogenesis of the neuropsychiatric manifestations remains unclear and poorly understood, but multiple hypotheses have been proposed, including CNS metabolic abnormalities, ischemia, demyelination, oxidative stress, free radical damage, PBG or ALA neurotoxicity, ALA promoting the generation of reactive oxygen species (ROS) which may result in oxidative damage to membrane structures within the central nervous system [5][42][43], ALA inducing lipid peroxidation in the cerebellum and hippocampus too [5][42], nervous tissue heme deficiency which may be deleterious for the synthesis of important heme proteins such as cytochrome P450 or nitric oxide synthase, inhibition of gamma-aminobutyric acid (GABA) release at central synapses by ALA, a heme-dependent enzyme, leading to increased levels of brain tryptophan and increased turnover of 5-hydroxytryptamine, a neurotransmitter, decreased activity of hepatic tryptophan pyrrolase, ALA inducing lipid peroxidation in the cerebellum and hippocampus too [5][42], nervous tissue heme deficiency which may be deleterious for the synthesis of important heme proteins such as cytochrome P450 or nitric oxide synthase, inhibition of gamma-aminobutyric acid (GABA) release at central synapses by ALA, a heme-dependent enzyme, leading to increased levels of brain tryptophan and increased turnover of 5-hydroxytryptamine, a neurotransmitter, decreased level of melatonin levels, which enhanced ALA-mediated lipid peroxidation [5][9][11][28][30][44].

Peripheral neuropathy, which is predominantly a motor neuropathy, initially affecting mainly the proximal rather than distal muscles, is next in order of frequency. Patients typically present with predominantly motor involvement, characterized by weakness and areflexia, which may mimic Guillain Barré syndrome, as in our patient. Sensory loss over the trunk is also common, although it is often overlooked. Cranial nerves can also be impaired in cases of AIP, with the facial and vague nerves being involved more than the others [12]. Porphyric neuropathy typically presents as a motor neuropathy of the axonal type [48][49]. The pathophysiology underlying axonal dysfunction in AIP remains unknown. Heme is an essential component of the mitochondrial electron transport chain and critical to aerobic metabolism and ATP production. Fast axonal transport is highly energy dependent, and diminished ATP availability would disrupt this process. The accumulation of neurotoxic heme precursors may lead to impaired function of the axonal Na⁺/K⁺ pump with consequent alteration in membrane potential to cause neuronal cell death and axonal degeneration [48].

The most common sign in acute porphyrinic attacks is tachycardia, which occurs in as many as 80% of patients with acute attacks. Tachycardia results, in part, from the release of catecholamine during an acute attack and has been implicated in the sudden death attributed to cardiac arrhythmias [12].

Our patient presented with hyponatremia which was constant during hospitalization. Marked hyponatremia frequently complicates acute porphyrias [5][11][21][28][35][38][52]. Its mechanism is not fully understood, but the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) [5][11][21][35][38][53], with resultant dehydration [21][54], nephrotoxicity [5][21], excess renal sodium excretion, and damage to the supraoptic nuclei of the hypothalamus, has been implicated in its pathogenesis [5][12][21].

The sub-fever (37°–38°C) and the leukocytosis were initially attributed to the main disease while repeated hemocultures, done during the fever attack, were constantly negative. Then, during the final state the prolonged fever syndrome (39°C) and the leukemoid reaction (leukocytosis with neutrophilia – 70000 leukocytes/mm³) were attributed to the bacterial infection with Acinetobacter (confirmed at the last hemoculture), sensitive only to Colyseitin, antibiotic avoided in persons diagnosed with AIP.

Acute renal failure may be a complication of an acute AIP attack. Vomiting or diarrhea as a result of an AIP attack can lead to hypovolemia, resulting in prerenal azotemia. Urinary retention may also cause a post obstructive uropathy. Excessive dosing of hemin may cause also reversible acute renal tubular damage [55–57].

Management

It is important to understand the pathogenesis, diagnosis, and management of porphyrias, because they often are misdiagnosed and therefore, mismanaged in treatable patients.

Prevention is the key. AIP patients should be advised to use as few drugs as possible. Drugs that are used should be “safe” based on experimental and clinical experience. Authoritative websites should be consulted to avoid exposure to harmful drugs in treating intercurrent illnesses or symptoms. Oral carbohydrate intake should always be adequate (a well-balanced diet somewhat high in carbohydrates – 60 to 70 percent of total calories) and starvation and fat diets should be avoided. Infections should be treated promptly. Stresses should be avoided if possible. Smoking cessation should be recommended. Relatives who are at risk for AIP should be screened for the disease, probably best done at
centers with special expertise in the diagnosis and management of porphyria [31].

Frequently recurring attacks confined to the luteal phase of the menstrual cycle can be prevented with GnRH analogue [15][17][59]. If treatment is effective after several months, low-dose estradiol, preferably by transdermal route, or a biphosphonate may be added to prevent bone loss and other side effects, or treatment changed to a low-dose oral contraceptive.

During pregnancy, hormonal changes, prolonged fasting due to hyperemesis, and several drugs can initiate an acute porphirinic attack. Mother’s mortality rates range from 27 to 42.5%. Symptomatic exacerbations are generally due to exposing the patients to certain drugs that can modify the course of pregnancy, resulting in abortion, preterm births, and other pregnancy complications. Up to 60% of pregnancy complications happen at the beginning, in early gestational ages. Nearly 15% of the complications occur during the second trimester and are generally severe. Although during the last weeks of pregnancy, women present high ALA and PBG levels in urine, in porphyrinic pregnant women the levels tend to be higher [60][61].

Hemin prophylactically administered once or twice weekly can prevent frequent, non-cyclic attacks of porphyria in some patients [15].

Treatment of porphyrias depends on the patients symptomatology [2][3][58][62]. After securing the patients airway, breathing, and circulation, the disease initially is managed by stopping exacerbating medications, treating the underlying infections or illnesses and gaining pain control with nonporphyrinogenic opiates [2][21][63–67].

Key principles of management are summarized in Table IV [18][31].

<table>
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<th>Table IV</th>
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<tbody>
<tr>
<td>Therapy of acute attacks of porphyria</td>
</tr>
<tr>
<td>✓ Remove inciting factors: alcohol, drugs, toxins, chemicals, smoking</td>
</tr>
<tr>
<td>✓ Nutritional supplementation: at least 300 grams glucose/day</td>
</tr>
<tr>
<td>✓ Frequent checks of neurologic status: especially watch for development of paresis of muscles of respiration</td>
</tr>
<tr>
<td>✓ Monitor for hypoventilation (rising arterial pCO₂), hyponatremia or hypomagnesemia and treat vigorously if found</td>
</tr>
<tr>
<td>✓ Intravenous heme: 3–4 mg/kg/day for 3–5 days</td>
</tr>
<tr>
<td>✓ Parenteral meperidine or morphine for pain</td>
</tr>
<tr>
<td>✓ Phenothiazines for nausea, vomiting, agitation, etc.</td>
</tr>
</tbody>
</table>

Treatment of AIP consists of 3 elements: eliminating all precipitating factors by discontinuing drugs or treating infections, starting a high-carbohydrate diet or glucose infusion, and starting a hemin infusion [21][58][70][71].

Mild attacks may be treated with general supportive measures. A minimum daily intake of 300 g of carbohydrates is also required during attacks. If oral intake is inadequate, carbohydrates should be administered intravenously. Glucose or another readily metabolized carbohydrate should be used (300–500 grams). Replace fluids, particularly if patients have poor oral intake or have been vomiting. Monitor patients for potential hyponatremia or hypomagnesemia and modify administration of electrolytes and water appropriately.

Tachycardia and/or systemic arterial hypertension can be treated cautiously with beta-adrenergic blocking agents such as propranolol or nadolol. Typical daily doses are 40–240 mg of propranolol or 60–120 mg of nadolol. Caution must be exercised when using beta blockers because hypotension and serious bradycardia have been reported even after low doses [18][69]. The tachycardia and hypertension can be quite unsteady.

Seizures are treated by careful correction of hyponatremia. Almost all anticonvulsivant drugs have at least some potential for exacerbating acute porphyrias. Clonazepam may be less harmful than phenitoin, barbiturates or valproic acid. Bromides, gabapentin, and vigabatin are safe [65–67].

Intravenous heme therapy is also effective in managing acute attacks; it can be administered as hematin. The usual dose consists of 3 to 5 mg hematin/kg body weight once a day for 3 to 5 days, beginning as soon as possible after onset of the attack [12][31][72–75]. These patients should be monitored for complications of coagulopathy, thrombophlebitis and hemolysis.

Cimetidine is a cost-effective alternative to hemin for treating acute attacks (uncontrolled observations). Cimetidine inhibits hepatic CYPs and can prevent experimental forms of porphyria induced by chemicals that are activated by CYPs. However, chemicals activated by CYPs are rarely, if ever, implicated in human AIP. Therefore, cimetidine cannot be recommended as an alternative to hemin [12][76][77].

Liver transplantation has been highly effective in patients disabled by recurrent attacks of AIP, this may be an option for severely affected patients without advanced motor weakness [78][79].

Long-term monitoring is necessary in patients with AIP while they are at risk for developing chronic renal failure and hepatocellular carcinoma.
If present, hypertension should be treated, nephrotoxic drugs avoided, and renal function monitored. Current recommendations are that patients over 50 with acute porphyrias, and especially those with continued elevations of ALA and PBG, should be screened by hepatic imaging at least annually for early detection of hepatocellular carcinoma [78] [79].

**CONCLUSION**

AIP is a rare but fatal disease and the physician must consider it in the differential diagnosis of any acute abdominal pain. Future research is needed to investigate new treatment options and to define clinical parameters to monitor treatment effects and outcome in patients with AIP.

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