CASE REPORT

Acute porphyria in an intensive care unit

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Porphyrias are rare hereditary metabolic disorders caused by the inactivity of certain enzymes that participate in heme synthesis. We report 3 cases in which porphyria debuted with acute episodes in young patients. As is often the case, diagnosis was delayed, and intensive care was required for severe encephalopathy. Symptoms improved rapidly after hemin therapy was started, but peripheral polyneuropathy persisted for several months in 1 patient. We report the first case of a porphyria-related seizure triggered by use of the morning-after pill (levonorgestrel). [Emergencias 2012;24:454-458]

Keywords: Acute porphyria. Seizure. Intermittent acute porphyria. Coproporphyria. Intensive care.

Introduction

The porphyrias are rare congenital metabolic disorders affecting the production of heme, the oxygen-binding group of hemoglobin. They are characterized by a deficiency of the enzymes involved in the synthesis of the heme group[1-3] (Figure 1). Classically they are classified as hepatic and erythropoietic according to localization of the enzyme defect. Clinically they are subdivided into cutaneous, acute or mixed. Porphyrin accumulation can cause dermal photosensitivity while acute porphyria is associated with high concentrations of the precursors of porphyrins, namely aminolevulinic acid (ALA) and porphobilinogen (PBG). Around 80% of patients with acute (and mixed) porphyria are asymptomatic, but when the disease manifests, crises or acute attacks may be so severe as to require admission to intensive care units (ICU). It is very important to recognize the origin of these crises to establish early treatment and thus avoid serious sequelae, partly iatrogenic. We present three cases in whom delayed diagnosis caused such clinical deterioration that they required ICU admission for severe encephalopathy.

Clinical cases

Case 1. A 29 year-old man attended the ED three times for abdominal pain, nausea, vomiting, constipation and dark colored urine. Physical examination showed diffuse abdominal pain, hypertension and tachycardia. Laboratory tests showed

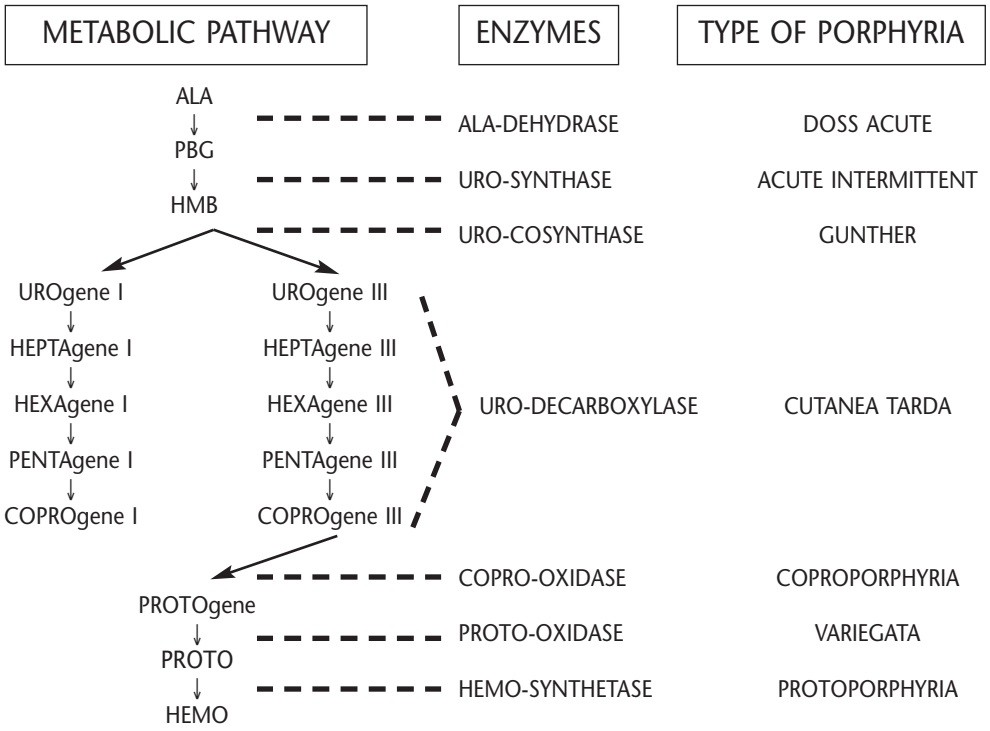

Figure 1. Heme biosynthesis and varieties of porphyria.

leukocytosis and hyponatremia of 128 mEq/l. Plain X-ray of the abdomen and brain CT-scan were normal. At 12 hours he suffered tonic-clonic seizure which resolved with diazepam. In the following 48 hours new neurological symptoms appeared, consisting of drowsiness, incoherent speech and hallucinations, along with seizure. Again brain CT-scan was normal. He was admitted to the ICU with stupor, weakness of the distal lower limbs, hyporeflexia, hypertension (170/90 mmHg) and tachycardia (120 beats/min), with severe abdominal pain that required opioid analgesia. Laboratory tests showed sodium 114 mEq/l and leukocytosis 23.000/mm^3 (91% neutrophils). Meningoencephalitis was ruled out by cerebrospinal fluid examination. A suspected diagnosis of porphyria was subsequently confirmed as coproporphyria by quantification of porphyrin in urine and feces and of the precursors ALA and PBG. Erythrocyte PBG deaminase activity was normal. Mutation N272H in the gene encoding for the enzyme coproporphyrinogen oxidase was detected. Family genetic study identified his mother as an asymptomatic carrier. Brain MRI showed hyperintense lesions in white matter (Figure 2), which showed decreased size in a second study a week later. Electromyography showed results compatible with axonal polyneuropathy. The patient responded favorably to treatment with glucose and hemin. At discharge from the ICU after 15 days, only impaired tendon reflexes persisted.

Case 2. A Romanian-born 39 year-old man with a recent history of upper airway infection attended the ED twice for abdominal pain, vomit-

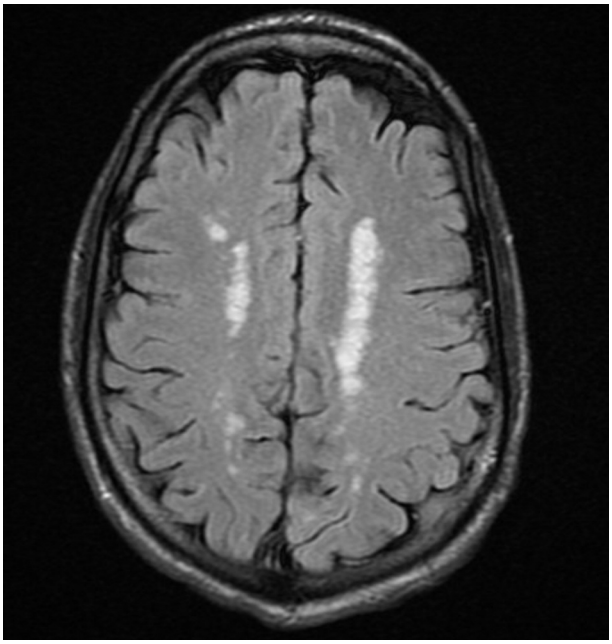

Figure 2. Brain MRI showing hyperintense lesions in the white matter during an attack of acute porphyria.

ing, dark urine, with no relevant clinical or laboratory findings. After 4 days he was readmitted for persistent abdominal pain and exacerbation. No relevant findings were noted on physical examination and laboratory tests showed a blood sodium level of 129 mEq/l. Abdominal X-ray and CT scan showed dilatation of the distal colon. Once admitted to the surgery department, the abdominal pain worsened but no evidence of causal pathology was found on intraoperative laparoscopy and colonoscopy. At 24 hours he presented neurological impairment which progressed to coma with flaccid tetraplegia and areflexia ; he was therefore transferred to the ICU where he was intubated and received mechanical ventilation. Laboratory tests showed accentuated hyponatremia to 113 mEq/l. Lumbar puncture ruled out meningoencephalitis. Rapid PBG urine test (Hoesch test) was positive. Porphyrinuria and elevated urinary elimination of ALA and PBG was repeatedly detected. Acute intermittent porphyria was diagnosed based on the finding of erythrocyte PBG deaminase activity of less than 50%. Genetic studies revealed the mutation R116W in the gene coding for this enzyme. Specific treatment was initiated with hemin and glucose, resulting in improvement of encephalopathy and the abdominal symptoms within days. However, axonal and demyelinating peripheral polyneuropathy persisted, with bilateral diaphragmatic involvement diagnosed by electromyography, which prolonged his ICU stay (5 months) due to the need for mechanical ventilation.

Case 3. A 28 year-old woman came to the ED several times during the previous months for abdominal pain, vomiting, malaise, and insomnia. She reported that two weeks before the first two episodes she had taken the "morning-after pill" (Levonorgestrel). She was treated with metoclopramide and metamizol. The following month she was admitted to the ICU for seizures. There, she presented marked hyponatremia (109 mEq/L), low plasma and high urinary osmolality, and a high concentration of plasma vasopressin, diagnosed as syndrome of inappropriate antidiuretic hormone (SIADH) secretion. The patient had tachycardia and hypertension. She was treated with fluid restriction and diuretics; serum sodium normalized and she was discharged, without diagnosis of the underlying disease. Six months later, she was readmitted for similar symptoms: abdominal pain, malaise and insomnia. Again, hyponatremia was detected. Her urine acquired a reddish hue, suggesting urinary infection and/or porphyria. Indeed, the concentration of urinary porphyrins and their precursors (ALA and PBG) was very high (coproporphyrin, 1016 µg/24 h; uroporphyrin, 3012 µg/24 h; ALA, 60 mg/L; PBG, 87 mg/L). Erythrocyte PBG deaminase enzyme activity was 50% and the mutation 669-698 of 30 was detected in the gene that encodes for this enzyme. A diagnosis of acute porphyria was established; the patient was treated with heme arginate with favorable outcome and she was discharged without neurologic sequelae.

Discussion

Acute intermittent porphyria, Doss porphyria and mixed porphyrias (coproporphyria and variegata) may manifest as crises or acute attacks. These porphyrias are therefore commonly grouped under the general heading of acute porphyrias[1-3]. The crises tend to be triggered by the action of factors such as fasting, stress, infections, hormonal changes, alcohol and other toxins and certain medications. These precipitating factors all consume or degrade heme. The potential neurotoxicity of such precursors and heme deficiency could be responsible for the crisis. Liver transplantation from donors with acute porphyria produces immediate neurotoxicity in non-porphyric recipients[4]. The list of drugs that can trigger crises in genetically predisposed individuals (Table 1) can be found at different web-sites (www.porphyria-europe.org). In this regard, it should be noted that metamizol, widely used in some countries, is dipyrone (a pyrazolone derivative).

The crises of acute porphyrias manifest with a wide variety of symptoms and nervous system dysfunction: autonomic (abdominal pain, hypertension and tachycardia), central (encephalopathy, seizures SIADH) and peripheral (peripheral polyneuropathy)[5]. Crises are the result of a wide combination of these symptoms which appear and progressively overlap if left untreated, and give rise to a varied clinical picture (Figure 3), which explains why this disease has been called “the little imitator"[6].

However, all these crises have a very similar debut. The initial symptom of diffuse abdominal pain is almost always present, associated with nausea, vomiting and constipation. Tachycardia and hypertension are usually also present, as is dark-colored urine due to uroporphyrins and other polypyrroles formed by non-enzymatic condensation of PBG (Figure 4).

If the picture progresses, central nervous system symptoms begin to appear, ranging from irri-

Table 1. Drugs most commonly associated with the onset of crisis in acute porphyrias

Barbiturates	Carbamazepine	Carisoprodol
Ergotamines	Hydantoins	Griseofulvin
Glutethimide	Methyldopa alpha	Methyprylon
Meprobamate	Pentazocine	Primidone
Pyrazolones	Pyrazinamide	Progestogens
Succinimides	Sulfonamides	

tability, insomnia and varied psychiatric manifestations to severe encephalopathy with decreased levels of consciousness and even coma. Generalized or partial seizures are frequent[7], which typically worsen with classical anticonvulsants such as phenytoin. A typical finding of varying severity is hyponatremia, attributed SIADH due to hypothalamus involvement[2,3]. The incidence of peripheral neuropathy is estimated at 10-40%[8]. This is predominantly motor, areflexic and with sensory symptoms and myalgia. Symptom severity and reversibility depends on how long it takes to initiate treatment.

Diagnosis is mainly based on clinical suspicion and the use of rapid tests, such as PBG in urine, which are easy to apply at the bedside[9]. The most widely used test is the Hoesch test for ease of application and availability (the reagent is preserved during months in a refrigerator). Two drops of fresh urine are added to 1 ml of Ehrlich reactant (2 g p-dimethylaminobenzaldehyde in 100 ml of 6N hydrochloric acid); the mixture turns pink-red if there are high concentrations PBG (Figure 5). There are no false positives due to high concentrations of urobilinogen, and a negative test virtually rules out an attack of acute porphyria. The

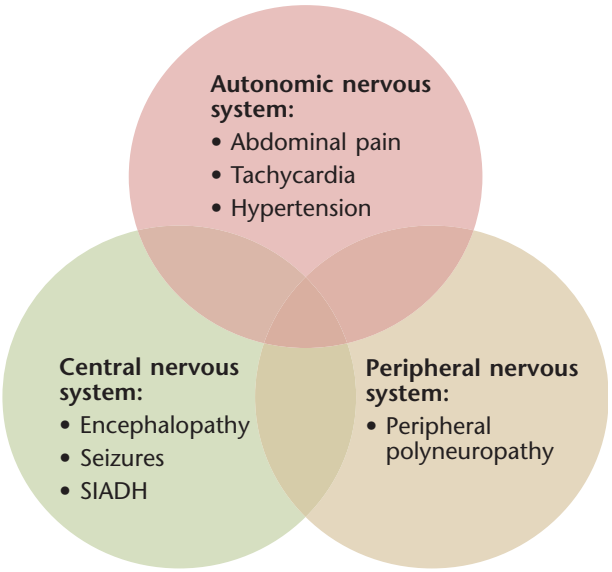

Figure 3. Symptoms of acute porphyria. SIADH: syndrome of inappropriate antidiuretic hormone secretion.

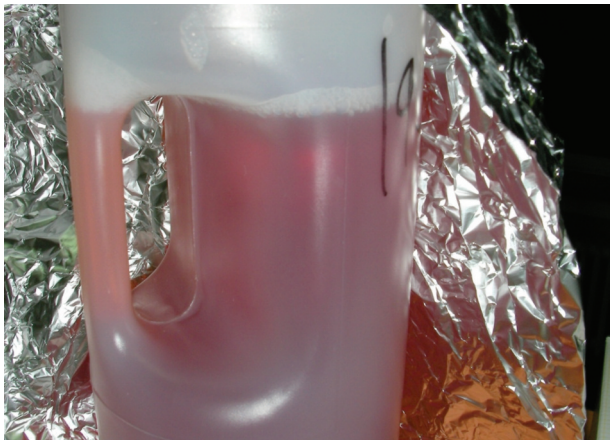

Figure 4. Urine of a patient with acute porphyria (coproporphyria).

rapid biochemical test does not establish a definitive diagnosis, and it is necessary to determine enzyme hypo-activity and the concentration of porphyrin precursors in urine, plasma and feces, and finally genetic studies are needed[10-12]. These tests should not cause a delay in initiating treatment. Differential diagnosis Guillain-Barré syndrome and heavy metal poisoning should be performed[13].

The objective of treatment is to reduce the pathological accumulation of precursors by exogenous administration of glucose and hemin, which regulate the activity of ALA synthetase by a negative feedback mechanism. The hemin dose is 3-4 mg/kg administered intravenously daily for 4 days. The glucose required is approximately 300 mg per day, preferably at 10% to minimize its effects on hyponatremia. Later, oral feeding can be initiated with a carbohydrate-rich diet. We do not have references concerning the possible use of tolvaptan to correct the hyponatremia.

Symptoms deriving from sympathetic hyperactivity respond well to treatment with beta blockers[14]. Seizures are more difficult to treat, but benzodiazepines and gabapentin[15] are safe drugs. Abdominal and neuropathic pain can be safely controlled using opioids.

It is especially important to avoid potential triggers of acute porphyria crises: fasting, stress, infections, tobacco, alcohol, progestins and drugs considered unsafe. Some patients have required liver transplantation due to the recurrence and severity of porphyria crises[16]. Gene therapy for exceptional cases is an ever closer possibility[17].

Although oral contraceptives are considered contraindicated in patients with acute porphyria, many patients have used them without effects[18]. However, the concentration of the levonorgestrel

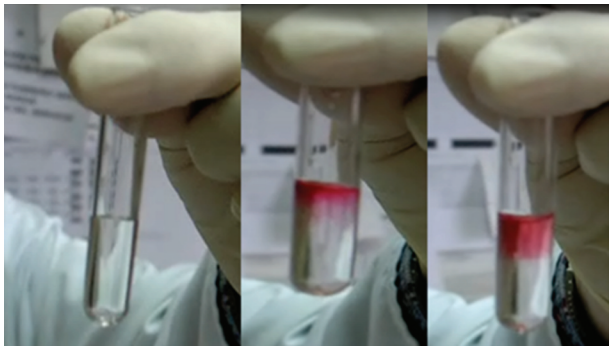

Figure 5. Test de Hoesch.

progestin is much higher in the "morning after pill" (1.5 mg). The peri-coital use of this drug is reasonably safe and effective in the general population, which perhaps has led to its abuse as a routine method of contraception[19] instead of exceptional use[20]. The fact that it triggered a crisis of acute porphyria in our patient leads us to consider that the "morning-after pill" should be contraindicated in acute porphyrias and this should appear in the informative leaflet.

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Porfirias agudas en la unidad de cuidados intensivos

Calvo de Mora Almazán M, Acuña M, Garrido-Astray C, Arcos Pulido B, Gómez-Abecia S, Chicot Llano M, González Parra E, Gracia Iguacel C, Pedro Alonso Alonso P, Egido J, Enriquez de Salamanca R

Las porfirias son enfermedades metabólicas hereditarias muy raras, causadas por la hipoactividad de determinadas enzimas implicadas en la síntesis del grupo hemo. Presentamos tres casos de pacientes jóvenes que debutaron con crisis de porfiria aguda, y en los que, como es frecuente, se retrasó el diagnóstico y llegaron a precisar ingreso en la unidad de cuidados intensivos (UCI) por encefalopatía grave. Tras realizar el tratamiento con hemina, la clínica mejoró rápidamente, pero en un paciente persistió una polineuropatía periférica grave como secuela durante meses. Además, comunicamos el primer caso de desencadenamiento de crisis porfírica por el uso de la "píldora del día después" (levonorgestrel). [Emergencias 2012;24:454-458]

Palabras clave: Porfirias agudas. Crisis. Porfiria aguda intermitente. Coproporfiria. Cuidados intensivos.