Porphyria: Case Report

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ABSTRACT

It is reported the case of a 22-year-old woman with acute intermittent abdominal pain accompanied by tachycardia, sweating, arterial hypertension, difficulty in walking, and muscular pains because of neuropathy. After multiple studies, there is a suspicion of porphyria when observing the change of urine color after being exposed to light for hours and the diagnosis is confirmed by auxiliary exams, such as porphobilinogen in urine. It is suggested that this acute attack of acute intermittent porphyria was due to the recent use of estrogens as a contraceptive method. Such pathology is uncommon, so its diagnosis is difficult.

Key words: Acute intermittent porphyria, Porphobilinogen.

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INTRODUCTION

Acute porphyrias are a group of metabolic diseases presented by enzymatic alteration that alter the metabolism of Heme group. There are some varieties: acute intermittent porphyria (as in the case described), variegate porphyria and coproporphyrin[1].

The clinical manifestations presented are non-specific, ranging from abdominal pain, as the most frequent symptom, to neurological alterations, such as neuropathy, autonomic dysfunction and endocrinological alterations, such as SIHAD. Many times it is not so simple to get a diagnosis[2].

CLINICAL CASE

Woman from Lima, 21 years old, student, single, with no personal or family history of importance, no recent trips in the last months, with three weeks of intramuscular contraceptive method (estradiol valerate / norethisterone enanthate). She reports having a disease of about two weeks starting with moderate, diffuse abdominal pain that did not give over to analgesics, with two admissions for emergency and even with surgery evaluation for probable surgical abdomen. During the last week the abdominal pain is accompanied by palpitations, sweating, generalized myalgia, and difficulty when walking.

The physical examination on admission showed blood pressure of 150/90 mmHg, heart rate of 135 beats per minute, profuse sweating in abdomen, diffuse, not-located pain at deep palpation, proximal muscle weakness, and hyper-reflexia.

Table 1 shows the auxiliary laboratory analysis. The sample for urine test showed no alterations, however, when leaving it for about 10 hours exposed to the sun's rays changed from light color to reddish color (see Figure 1).

Tabla 1. Laboratory tests.

Hemoglobin: 12 mg/dl
leukocyte: 7 500 cel/mm3
Platelets : 200 000 cel/mm3.
Urea: 10 mg/dl
GOT: 53 U/l
GPT: 58 U/l
FA: 234 mg/dl
LDH: 327 mg/dl
Calcium: 8,9 mg/dl
ESR: 11 mg/dl
Total CPK: 0,52 U/l
TSH: 1,8 µU/ml
Sodium: 128 mmol/L
VDRL, HIV, HBsAg: non-reactive tests.
Determination of lead in blood: 2.34 (<20) µg/dl

Figure 1. ALA excretion increases less than PBG. Its measure is not essential to establish a diagnosis of Porphyria, but it is commonly combined with PBG and may be useful for making the difference from other causes of abdominal pain.

Abdominal ultrasound: Liver, pancreas, and spleen of normal characteristics, without evidence of mass or free liquid.

Tomography: Liver of normal size and shape. There is no hypodense image with peripheral contrast uptake in segment VII, suggestive of hepatic hemangioma, the rest of structures are normal, presence of reactive nodes in the right iliac fossa. Electromyography: Axonal polyradiculopathy with signs of activity.

With the clinical history and laboratory tests (see Table 2), the diagnosis of acute intermittent porphyria is made. Hydration with 10% dextrose begins, pain

management, and propanolol for the control of dysautonomia. The corresponding procedure for the purchase of Hematyna is performed.

Tabla 2. Analisis de laboratorio confirmatorios de la enfermedad.

Porfobilinógeno (orina): 54,9 (valores normales: 0,0 - 3,40) mg/24h
Acido delta-aminolevulínico: 40,3 (valores normales: 1,50 – 7,50) mg/24h

Now it is reviewed the main pathogenic, clinical, diagnostic aspects, as well as the specific treatment for the disease.

DISCUSSION

Porphyria is a rare hereditary metabolic disease due to a deficiency of hydroxymethylbilan synthase (HMBS) in the biosynthesis of Heme group. The prevalence of genetic carrier is estimated at 1/10 000 inhabitants, but the prevalence of cases is only from 1 to 5 per 100 000 inhabitants[3].

Porphyria appears after puberty with occasional neuropsychiatric crises associated to the accumulation of porphyrin precursors, such as aminolevulinic acid -δ (ALA) and porphobilinogen (PBG) which are released from the liver into the circulation[1].

Several exogenous and endogenous factors induce the biosynthesis of Heme group through the direct or indirect activation of ALA synthase. In patients with AIP with hereditary deficiency of HMBS, this results in the accumulation of neurotoxic porphyrin precursors (ALA and PBG) in the tissues and circulation which give clinical manifestations[4]. Heme is the end product of the Heme biosynthetic pathway, regulates the transcription of ALA synthase through negative feedback which would decrease precursor levels. Therefore, it can be used in the treatment of an acute attack[4].

Manifestations

Most of the acute attacks are manifested as a combination of abdominal pain, mild mental symptoms, and autonomic dysfunction which occurs with tachycardia, hypertension, and sweating. They may develop peripheral neuropathy and severe encephalopathy if an acute attack occurs[5]. In general, acute attacks are triggered by both endogenous and exogenous factors, such as certain medications, alcohol, infections, low caloric intake, or changes in sex hormones during the menstrual cycle or pregnancy. All of these factors induce Heme synthesis, either directly or indirectly, through the activation of ALA synthase in the liver resulting in the accumulation of porphyrin and its precursors in tissues and circulation[5]. Progesterone is known to be a potent inducer of ALA synthase. Cyclic attacks occur primarily in the premenstrual phase, when estrogen and progesterone levels fluctuate more, and are usually solved during early menstruation. Individual variation in progesterone metabolism can play a role on the clinical manifestations of porphyria. Cytochrome P450 activities in the liver also vary individually and may result in an abnormal level or sex hormones ratio affecting the feedback mechanism for hypothalamus[6]. In this case, the patient initiated the use of progestogens as a contraceptive method and we consider that this was the triggering factor.

Excess of ALA is the cause of neuronal damage and could be responsible for neuropathy and encephalopathy and autonomic dysfunction through multiple mechanisms. The results of experimental and clinical data support the direct neurotoxicity of ALA, as well as the modification of γ-aminobutyric acid (GABA) adrenergic system, due to the structural similarity of ALA and GABA/glutamate, and the formation of free radicals and reactive species of ALA oxygen may play a role on the pathogenesis of an acute attack[7].

Clinical criteria for an acute attack include the paroxysmal nature of abdominal or back pain symptoms associated to one or more signs of autonomic dysfunction, hyponatremia, muscle weakness, or mental symptoms. In case of suspicion, it should be dosed porphobilinogen (PGB).

Las concentraciones de PBG en orina son al menos diez veces el límite superior de la normalidad dentro de la semana de la aparición de los síntomas[3]. En estas concentraciones, las muestras de orina pueden presentar un color rojo parduzco al estar de pie, o la orina puede ser de este color cuando

está fresca, pero esta coloración, que se produce por condensación de PBG a porfobilina, porfirina y otros compuestos, es variable y no siempre observada[8]. Este evento se pudo apreciar en la paciente.

Concentrations of PBG in urine are at least ten times the upper limit of normal level within the week symptoms appear[3]. At these concentrations, urine samples may be brownish-red when standing, or urine may be of this color when it is fresh, but this coloration, produced by condensation from PBG to porphobiline, the porphyrin and other compounds, is variable and not always observed[8]. This event could be seen in the patient.

The excretion of PBG decreases as the attack is solved. In AIP, the excretion usually remains increased for many weeks, but in VP and HCP it may return to normal levels or to a close value within a week or more after symptoms appear[9].

It should be noted that the abnormal metabolism of porphyrin and its precursors can also be detected in patients with hepatopathy or heavy metal poisoning[10]. Clinical manifestations may even resemble acute intermittent porphyria.

The management includes supportive and specific treatment. The supportive treatment includes management of abdominal pain with morphine or pethidine. Hypertension and tachycardia are treated with propanolol. Hyponatremia, that is often the cause of seizures and vomiting, should be solved with promazine. These are considered safe drugs in the management of porphyria[3].

The treatment of acute attacks with a diet high in carbohydrates or infusions (300 to 500 g / day) has been used in order to decrease ALA synthase activity and to avoid the fasting. The use of 5% based dextrose solution, or two liters of normal saline solution with 10% to 20% of glucose given in doses divided in 500 ml for 24 hours through a central venous catheter may be indicated[11].

The specific management uses Heme preparations, which lead to a fast decrease in the synthesis of porphyrin precursors through the negative feedback of the reduced transcription of ALA synthase in the liver achieved by the results of Heme group. The cessation of an acute attack occurs a few days after administration[12].

In Europe, Asia, and South Africa, hemin is commercially available as heme arginate (Normosang®, Orphan Europe SARL, Puteaux, France) and in North America as lyophilized hematin (Panhematin®, Ovation Pharmaceuticals Inc., Deerfield, IL, USA)[13].

The recommended dose is 3 mg/Kg of body weight up to 250 mg administered on each of the four consecutive days. A dose of 250 mg is often convenient to use for adults regardless of the weight[8,12]. Thrombophlebitis is considered within adverse effects[14].

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Nothing.

CONFLICTS OF INTEREST

The authors do not report conflicts of interest regarding the present manuscript.

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