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Acute intermittent porphyria: Long-term follow up of 35 patients☆

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ABSTRACT

Background and objectives: Acute intermittent porphyria (AIP) is a rare disease that results from a deficiency of porphobilinogen deaminase, the third enzyme of the heme biosynthetic pathway. AIP carriers are at risk of presenting acute neurovisceral attacks associated with overproduction of heme-precursors in the liver.
Patients and method: We report the characteristics of all AIP patients attended in the Hospital Clinic of Barcelona during the years 1993–2013 and their long-term follow-up.
Results: Thirty-five AIP patients (33 women, 2 men) experienced acute attacks. Treatment with hemin resolved the acute neurovisceral crisis in all cases. Nine patients presented peripheral neuropathy and persistent sequelae. Long-term follow-up allowed classifying the patients into groups: A, patients with acute symptoms during 1–2 years and subsequent long-lasting clinical remission (n = 24) or a few sporadic crises (n = 3), and B, patients with recurrent attacks requiring chronic administration of hemin (n = 8). In a majority of the patients of group A, the urinary excretion of heme-precursors decreased gradually over time. However, the chronic hemin regime did not induce a decline of urinary heme-precursors in the patients of group B. Additionally, we identified 44 asymptomatic AIP carriers, most (70.5%) with normal values of heme-precursors in urine.
Conclusions: A majority of the AIP patients of our series achieved a long-lasting clinical remission. A minority (23%) presented recurrent attacks that required chronic hemin infusions without feasible interruption and without long-term biochemical remission. The type of mutation within the porphobilinogen deaminase gene and also life-style related factors may determine remission time-course.

Porfiria aguda intermitente: seguimiento a largo término de 35 pacientes

Palabras clave:
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Porfobilinógeno deaminasa
Crisis neurovisceral

RESUMEN

Fundamento y objetivos: La porfiria aguda intermitente (PAI) es una enfermedad causada por un defecto en la enzima porfobilinógeno deaminasa que cataliza la tercera etapa de síntesis del hemo. Los portadores pueden presentar ataques neuroviscerales agudos tras sobreproducción hepática de precursores del hemo.
Pacientes y método: Se presentan las características de todos los pacientes con PAI atendidos en el Hospital Clínic de Barcelona entre los años 1993-2013, y su seguimiento a largo plazo.
Resultados: Treinta y cinco pacientes con PAI (33 mujeres y 2 varones) presentaron ataques agudos neuroviscerales. El tratamiento con hemina resolvió el cuadro agudo en todos los casos. Nueve pacientes presentaron polineuropatía y secuelas persistentes. El seguimiento permitió clasificar a los pacientes en: A, con sintomatología aguda durante 1-2 años y posterior remisión duradera (n = 24) o bien alguna crisis puntual (n = 3), y B, con ataques recurrentes que requirieron administración crónica de hemina (n = 8). En la mayoría de los pacientes del grupo A la concentración urinaria de precursores del hemo fue disminuyendo progresivamente, mientras que en el grupo B esta se mantuvo elevada sin descenso observable

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a largo término. Adicionalmente, el estudio familiar permitió identificar 44 portadores asintomáticos, la mayoría (70,5%) con valores normales de precusores del hemo en orina.
Conclusiones: Una mayoría de pacientes con PAI de nuestra serie logró una remisión clínica duradera. Una minoría presenta ataques recurrentes, sin que el tratamiento crónico con hemina haga factible su interrupción ni induzca remisión bioquímica a largo plazo. El tipo de mutación en el gen de la porfobilinógeno deaminasa, y también factores asociados al estilo de vida, pueden determinar el curso de la remisión.

Introduction

Acute intermittent porphyria (AIP) is a disease caused by a defect in the enzyme porphobilinogen deaminase (PBGD; also called hydroxymethylbilane synthetase, EC 2.5.1.61), which catalyses the third step of heme synthesis.[1] The enzyme deficiency results from the existence of mutations in the *PBGD* gene located at chromosomal region 11q24.1 and consisting of 15 exons.[2] The disease is transmitted in an autosomal dominant way with a low clinical penetrance, although, so far, this has not been accurately estimated.

The annual incidence of new cases in most European countries has been estimated at 0.13 per million inhabitants, except in Sweden, which has a higher incidence due to founder effects and genetic migration.[3] Subjects who carry the genetic defect have potential risk of very severe acute neurovisceral attacks. This is much more common in women than in men, and never happens before puberty.[4,5]

In its active mode, AIP is in the form of an acute dysfunction of the central nervous system (CNS), autonomic and peripheral (PNS).[6] Patients come to the emergency room with acute abdominal pain, tachycardia, hypertension, seizures, psychiatric disorders, and hyponatremia. PNS involvement can induce motor neuropathy, which can cause tetraparesia and even respiratory paralysis. The clinical features are associated with a sharp hepatic overproduction of heme precursors, porphobilinogen (PBG) and delta-aminolevulinic acid (ALA) after induction of the ALA synthetase 1 *(ALAS1) gene*. According to the most plausible pathophysiological explanation, ALA hepatic export and the resulting cellular toxicity could be the cause of neurological crises.[7]

The acute attacks result from the concomitance of the genetic/enzymatic underlying defect and hormonal or other precipitating factors (hypocaloric diet, stress, drug administration, infections, etc.) that can induce expression of the *ALAS1* gene in the liver.[7] The abrupt induction of the first part of the metabolic pathway, coupled with liver PBGD underactivity, results in PBG and ALA accumulation. The *ALAS1* gene is partly controlled by a heme negative *feedback* mechanism, last product of the metabolic pathway.[2] In case of acute attack, the intravenous administration of hemin (human hemin stabilized with arginine, Normosang®), which restores the hepatic heme reserve and reduces *ALAS1* induction is a measure of high therapeutic effectiveness that, in most cases, resolves neurovisceral crises, although not allowing a complete biochemical remission.[5] The administration of glucose also has an inhibitor *ALAS1*[2] effect (though less effective).

A minority of patients with AIP experience recurrent attacks requiring repeated heme administration for long periods of time. Liver transplantation has taken place in some very severe recurrent cases. In these cases, the transplant has cured the disease, thus demonstrating its hepatic origin.[8]

Our study is the summary of the experience (expanded over several decades) in the diagnosis, treatment and research of the AIP in the Porphyria's Unit (Department of Dermatology and Biomedical Diagnostic Centre) of the Hospital Clínic of Barcelona. All the cases treated in this unit between 1993 and 2013 are presented herein, together with a description of their clinical and biochemical characteristics. The prevalence of the disease in our country has been estimated, as well as a list of precipitating factors and a progression categorization of recurrent cases.

Patients and method

Demographic, clinical, biochemical and family data of all patients with AIP who were treated consecutively by the Porphyria's Unit of the Hospital Clínic of Barcelona between the years 1993 and 2013 were collected. During this period, 35 patients were treated and 94 relatives were studied.

AIP diagnosis in patients was made according to the criteria agreed by the *European Porphyria Initiative*.[9] These criteria include: characteristic clinical symptoms, significant PBG, ALA and urine porphyrins increase, fluorescence emission peak in plasma, porphyrins and isomers high-performance liquid chromatography in stool, decreased PBGD enzyme activity in red blood cells and, finally, confirmation by PBGD gene mutation detection.[10]

The classification criteria in clinically asymptomatic relatives had to do with the presence of *PBGD* gene mutation and a low activity in the PBGD enzyme in blood.

Results

35 new patients were identified with AIP during 20 years of observation, acting as the reference porphyria unit in Catalonia (from 6.0 to 7.5 million during this period). This would mean, as a tentative calculation (and with reference to an average population of 7 million inhabitants) an average incidence of 0.25 new cases/million inhabitants-year.

The disease incidence was shown to be highly dependent on gender (33 women versus 2 males).

The 35 patients had clinical symptoms which started as abdominal pain, nausea, vomiting and intestinal paresis, all accompanied by hyponatremia and other vegetative signs such as tachycardia and increased blood pressure, and emission of dark urine (Table 1).

In 26 cases, clinical symptoms were reduced to autonomic type alterations. However, 9 patients also had altered PNS presented as ascending polyneuropathy with tetraparesis, along with anxiety, insomnia and psychomotor agitation. In 5 of these last cases, CNS involvement was also present in the form of seizures, confusional state and hallucinations. It is noteworthy that the 9 cases who developed this severe neurological condition experienced a delay of several months or even years in the diagnosis of porphyria,[11] being treated during that time with porphyrinogenic drugs such as dipyrone or hydantoins, which could have worsened the clinical features.

Precipitating factors of the first acute porphyria crisis are reflected in Table 2. It should be noted that crisis development is associated with a high incidence of stress and the fact that 60% of cases involve the coincidence of 2 or 3 causing factors.