

# Psychiatric complications of a late diagnosis of acute porphyria in an affected male

Gabriela Elizondo Cárdenas,<sup>1</sup> María Dolores Hernández Almaguer,<sup>1</sup> Ricardo Rangel Guerra,<sup>2</sup> María Georgina Arteaga Alcaraz<sup>1</sup>

Artículo original

## SUMMARY

### Introduction

Acute porphyrias are rare genetic disorders of incomplete penetrance (10%). This means that only 10% of the individuals with the genotype known to cause the disease will show any signs or symptoms of such disease. They consist of a deficiency of any enzyme of the heme biosynthesis and are considered as exceptional inborn errors of metabolism with an autosomal dominant inheritance. The incidence is 1 in 100 000. The symptoms are variable and unspecific, consisting mainly of severe abdominal pain, tachycardia, and hypertension. Other frequent manifestations are psychiatric symptoms like depression, psychosis, and hallucinations. In addition to these unspecific symptoms, patients may also present peripheral neuropathy and loss of sensation, which can become permanent. In severe cases, liver damage and chronic renal disease can occur. The objective of this study is to highlight the importance of the difficult diagnosis of acute porphyria, the implications of a misdiagnosis, and the importance of adequate treatment.

### Case

We present a 47 year-old male with a history of abdominal pain for seven years. The pain was diffuse, progressive, and incapacitating. He was diagnosed and treated for chronic gastritis and cholecystitis without improvement. An elective cholecystectomy was performed but he continued with intense abdominal pain. Three years later he developed hallucinations, paresthesias, muscular weakness, depression, and irritability. He was managed as a psychiatric patient with psychotic tendencies. After a complete and thorough history of all his symptoms throughout the years and a re-examination of the patient, acute porphyria was considered as a possible diagnosis. Specific laboratory studies were indicated revealing elevated levels of porphyrines, elevated levels of PBGD, PBG in urine within normal levels, elevated presence of coproporphyrines by chromatography, and a normal PBGD enzymatic activity. The diagnosis of acute porphyria was established. Appropriate treatment was initiated starting with adequate pain management. A high carbohydrate diet was also recommended with appropriate nutritional requirements and caloric intake. Another important aspect of the management was the elimination of risk factors, like alcohol, cigarette smoking, and certain specific medications. Follow-up showed significant

improvement of his symptoms and less frequent acute attacks with identification and elimination of risk factors. He was able to return to a stable work schedule. The patient presents residual permanent renal damage. Adequate doctor-patient education was maintained.

### Discussion

This case is an important example of a not-so-rare genetic disease that any physician should have in mind when confronted with a patient with unspecific paroxysmal clinical manifestations. The possibility of acute porphyria should always be excluded before establishing a diagnosis of a psychiatric illness. Prompt diagnosis and management are crucial to reduce the risk of recurrences and permanent damage. Patient education is a very important aspect of the management of the disease since there is no cure. There is a specific treatment for the management of acute attacks (Hemin) but, unfortunately, it is still unavailable in our country. This is a problem that turns the management and prevention of risk factors into the most important tools we have to improve our patients' quality of life.

**Key words:** Psychosis, porphyria, heme, coproporphyrin.

## RESUMEN

### Introducción

Las porfirias agudas son un conjunto de enfermedades genéticas de penetrancia incompleta (10%). Es decir, sólo 10% de los individuos con el genotipo determinado que causa la enfermedad presentan algún signo o síntoma de ella. Las porfirias agudas son causadas por una deficiencia de alguna de las enzimas de la biosíntesis del heme. Son unos de los pocos errores innatos del metabolismo que presentan herencia autosómica dominante. La incidencia es de 1 en 100 000, y es más común en mujeres de entre 30-40 años. Los síntomas son variables e inespecíficos; los más comunes son: dolor abdominal difuso e incapacitante, taquicardia e hipertensión. También se acompaña de síntomas psiquiátricos como depresión, intento de suicidio, paranoia y alucinaciones. Otros síntomas relacionados son neuropatía periférica y pérdidas sensitivas, daño hepático e insuficiencia renal crónica. El objetivo de este estudio es establecer la importancia de realizar un diagnóstico oportuno de porfiria aguda, ya que un diagnóstico erróneo puede generar tratamientos y gastos innecesarios al

<sup>1</sup> Department of Genetics, Universidad Autónoma de Nuevo León. Nuevo León, México.

<sup>2</sup> Department of Neurology, Universidad Autónoma de Nuevo León. Nuevo León, México.

Correspondence: Gabriela Elizondo Cárdenas. Departamento de Genética, Facultad de Medicina, UANL. Ave. Francisco I. Madero y Dr. Eduardo Aguirre Pequeño SN, Col. Mitras Centro, 64460, Monterrey, Nuevo León, México. Teléfono/Fax: (81)8329-4217 y (81)8348-3509. gabrielaec@gmail.com

Recibido primera versión: 26 de junio de 2008. Segunda versión: 7 de enero de 2009. Aceptado: 24 de marzo de 2009.

paciente. El diagnóstico de porfiria permite llevar a cabo un manejo y tratamiento adecuados que favorecen un buen pronóstico.

#### Caso

Se trata de un paciente masculino de 47 años de edad, sin antecedentes familiares relacionados, que presenta dolor abdominal intenso, difuso e incapacitante con siete años de evolución. Fue tratado como gastritis aguda y colecistitis. Se realizó colecistectomía sin lograr mejoría de los síntomas. Tres años después, se agregaron a los síntomas originales los siguientes: alucinaciones auditivas, parestesias, debilidad muscular, depresión e irritabilidad, por lo que se catalogó como paciente con trastorno psiquiátrico con tendencia psicótica. Se realizó historia clínica de todos los síntomas y una exploración física completa, por lo que se sospechó porfiria aguda. Se realizaron estudios de laboratorio específicos con los que se confirmó el diagnóstico de porfiria aguda por la presencia de niveles elevados de porfirinas en orina, niveles elevados de PBGD, niveles normales de PBG en orina, niveles significativamente elevados de coproporfirinas por cromatografía y actividad enzimática de PBGD en rangos normales. Se inició un tratamiento para el manejo adecuado del dolor. También, una dieta alta en carbohidratos, con aporte calórico adecuado. Se recomendó la eliminación de factores de riesgo como alcohol, cigarro y medicamentos específicos. Dos meses después se observó una mejoría significativa de los síntomas, control de crisis e identificación y eliminación de factores precipitantes. Los

síntomas psiquiátricos desaparecieron y el paciente pudo reestablecer sus actividades laborales y sociales. El paciente presenta hasta el momento datos de insuficiencia renal crónica. Se continúa el seguimiento del paciente.

#### Discusión

El caso presentado representa un ejemplo de una enfermedad genética que todo médico debe tener en mente cuando se presenta un paciente con síntomas inespecíficos. El diagnóstico de porfiria aguda es un diagnóstico de exclusión, pero sigue siendo importante en el análisis del diagnóstico diferencial. Es de gran importancia descartar o confirmar un caso de porfiria aguda antes de establecer el diagnóstico de un trastorno psiquiátrico. Establecer un diagnóstico temprano y un tratamiento específico mejora el pronóstico y limita el daño, particularmente neurológico y hepático. La educación del paciente es de extrema importancia, ya que no existe cura para la porfiria aguda. Una prevención que evite los factores precipitantes conocidos es uno de los tratamientos principales de esta enfermedad, ya que el medicamento específico para el control de la crisis aguda (Hematina) no se distribuye en nuestro país. Aunado a un subdiagnóstico de la enfermedad, lo anterior vuelve aún más difícil el manejo de los pacientes.

**Palabras clave:** Psicosis, porfiria, heme, coproporfiria.

## INTRODUCTION

Acute porphyrias are a group of genetic disorders of autosomal dominant inheritance with incomplete penetrance (10%). This means that only 10% of the individuals with a genotype known to cause the disease will show any signs or symptoms of it. These are considered among the few autosomal dominant inborn errors of metabolism since they are disorders of the heme biosynthesis.<sup>1</sup> The incidence is 1 in 100 000. They are more frequent in women since a major risk factor is a variation in hormone levels, for example pregnancy.<sup>2</sup> The age of presentation is around the third and fourth decades of life.<sup>2</sup> Acute attacks are variable, unspecific and may be life threatening.<sup>3</sup> The more frequent symptoms are severe abdominal pain, tachycardia, and hypertension. Other common manifestations are psychiatric symptoms like depression, suicide, psychosis, and hallucinations. Porphyria can be also complicated by other clinical manifestations such as peripheral neuropathy and loss of sensation, liver damage, and chronic renal disease.

Seventy-four percent of the patients will not have recurrences and can manage a normal life, but if the crises are not controlled, the risk of hepatic insufficiency and permanent neuropathic damage is high.<sup>3</sup>

The objective of this study is to highlight the importance of the difficult diagnosis of this disease, the implications of a misdiagnosis, and the importance of adequate treatment to improve the quality of life for these patients.

## CASE REPORT

We present a 47 year-old male patient with no relevant family history and no medical or psychiatric history, who suffered from abdominal pain for a period of seven years. The pain was described as progressive, incapacitating, and unresponsive to several prescription pain medications. He was diagnosed and treated for chronic gastritis and cholecystitis. A cholecystectomy was performed revealing no inflammation or pathology. His symptoms did not improve. Throughout the years, he consulted several doctors but none was able to explain or ameliorate his symptoms. Three years later, he presented memory problems and auditory hallucinations. Later, he developed paresthesias in all extremities, muscle weakness, depression, irritability, and anxiety. Because of these manifestations, a psychiatric ailment was considered. Psychotherapy and treatment were recommended but, due to poor patient cooperation, appropriate psychiatric evaluation was not done.

After a careful review of his medical history and a thorough physical examination which considered all his symptoms throughout the years, porphyria was suspected. Several specific laboratory studies revealed the following: porphyrines in red blood cells 89.65ug/100 (30-60ug/100), plasma porphobilinogen deaminase (PBGD) 40.7nmol/sec/L (15.8-29.8nmol/sec/L), porphobilinogen (PBG) in urine 0.2mg/24h (0-2.5mg/24h), plasma aminolevulinic acid (ALA) 4.179mg (0-4mg ALA/L), elevated presence of coproporphyrines by chromatography, and a normal PBGD enzymatic activity.

The diagnosis of acute porphyria was established. The patient was admitted at a hospital and received medical treatment for pain control. He was given a high carbohydrate diet. Patient education consisted in avoidance of certain foods, medications, and substances, for example: alcohol, cigarette smoking, and anticonvulsants. We recommended also minimal sun exposure. He improved significantly with sertraline and benzodiazepine. The frequency and intensity of his acute attacks diminished. He was able to identify and eliminate precipitating factors. To date, he has not presented another episode of auditory hallucinations. His sleep pattern normalized as well.

All the psychiatric symptoms disappeared eventually and he was able to return to a stable work schedule. However, since the right diagnosis was made only after the disease had already progressed, permanent neurological and renal damage were left. He has peripheral neuropathy and chronic renal disease under surveillance.

## BRIEF OVERVIEW OF ACUTE PORPHYRIAS

Each porphyria results from the deficient activity of a distinct enzyme of the heme biosynthesis. Four of the five hepatic porphyrias present themselves with acute attacks and neurologic and psychiatric manifestations. These porphyrias are: acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and 5-aminolevulinic acid (ALA)-dehydratase porphyria (ADP).<sup>4</sup> Table 1 shows their main genetic and enzymatic features. The major manifestations are neuropathic abdominal pain, peripheral neuropathy, and mental disturbances.<sup>1</sup> These develop in adult life, are more common in women than in men,<sup>5</sup> and are treated by methods to restore heme homeostasis. Variegate porphyria and hereditary coproporphyria can also cause lesions on sun-exposed skin.<sup>6,7</sup> These four types of acute porphyrias are indistinguishable from one another during acute attacks. Skin lesions are not present in all patients with HCP and VP. These dermatologic manifestations are present only in one-half of the patients with VP and one-third of the patients with HCP.<sup>8</sup>

Acute porphyrias are distinct from other porphyrias because of their common overproduction of the porphyrin

precursors ALA and porphobilinogen. This biochemical feature is important for the diagnosis and has implications in the pathogenesis of the neurologic manifestations.<sup>3,9</sup>

As shown in table 1, the enzyme deficiency is only partial. The remaining enzyme activity is usually sufficient to maintain heme homeostasis. These enzymatic defects generate susceptibility to the effects of precipitating factors, including many drugs (barbiturates, valproic acid, carbamazepine, cloroquine, sulfonamides, pyrazolones, griseofulvine, progestins, etc.), endogenous steroid hormones, fasting, dieting, smoking, alcohol, stress from illness, all of which increase the demand of hepatic heme in the heme biosynthetic pathway.<sup>4,9</sup> The intermediates accumulate in the liver.<sup>10</sup>

The mechanism of the neurologic damage is not completely understood. Accepted hypotheses suggest that the symptoms result from the porphyrin precursors themselves rather than a deficiency of the heme in nerve tissue.<sup>4,9</sup> It is suggested that the neuropathy is caused by demyelination and occasional axonal degeneration. Chronic symptoms and signs may reflect previous, unresolved neurologic damage.<sup>9</sup> Psychiatric manifestations are even less understood. It is uncommon to find brain abnormalities in diagnostic imaging tests. That is why these studies are not routinely done in patients with porphyria.

Approximately 90% of the carriers of a gene mutation for acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria remain asymptomatic throughout their entire lives.<sup>3</sup> And 74% have one acute attack throughout their lifetimes.<sup>4</sup> In a particular patient, the recurrent attacks tend to be similar and are more easily diagnosed over time. Pregnancy is usually well tolerated in women with acute porphyria.<sup>5</sup>

One of the most commonly reported clinical manifestations is severe neuropathic abdominal pain, which is diffuse and often accompanied by nausea, vomiting, distention, constipation, or diarrhea.<sup>1,11</sup> Other symptoms are insomnia, tachycardia, hypertension, seizures, hallucinations, depression, irritability, anxiety, and other acute psychiatric symptoms.<sup>4</sup> Sudden death, presumably from cardiac arrhythmia, may also occur during an acute attack. Peripheral neuropathy (motor) usually develops. Paresis is progressive and symmetrical in both extremities. Weakness may progress to respiratory and bulbar paralysis

Table 1. Characteristics of acute porphyrias

Disease (abbreviation)	Inheritance	Deficient enzyme	Subcellular locations	Enzyme activity %	Gene locus
Acute Intermittent Porphyria (AIP)	Autosomal dominant	PBG deaminase	Cytosolic	50	11q23.3
Hereditary Coproporphyria (HCP)	Autosomal dominant	Coproporphyrinogen oxidase	Mitochondrial	50	3q12
Variegate porphyria (VP)	Autosomal dominant	Protoporphyrinogen oxidase	Mitochondrial	50	1q22
ALA-dehydratase deficient porphyria (ADP)	Autosomal recessive	ALA dehydratase	Cytosolic	5	9q34

and death. Long-term complications include chronic arterial hypertension, chronic renal disease, chronic liver damage, and hepatocellular carcinoma.<sup>10-12</sup> There is also an increased risk for suicide.

As mentioned before, there are specific exacerbating factors. These include many drugs (phenobarbital, alcohol, ergots, estrogens, rifampin, sulfonamides, etc.) that increase the demand for hepatic heme, like cytochrome P450 enzymes. Other exacerbating factors are marked reductions in caloric or carbohydrate intake. Estrogen and progesterone are other exacerbating factors and explain why the attacks are more frequent in women.<sup>2</sup> Cigarette smoking, metabolic stress induced by infections, or surgery may lead to acute attacks.

The diagnosis of acute porphyria requires speed and accuracy because delayed treatment can result in permanent neurological damage and even death.<sup>5,13,14</sup> It is recommended to consider acute porphyria when the prominent symptoms include abdominal pain, which an initial clinical evaluation fails to identify a cause. In this case, the diagnosis of porphyria was considered after seven long years of pain and expensive, unresponsive search and treatments, including an unnecessary surgery.

It is important to consider acute porphyria when abdominal pain is accompanied by other classical symptoms; for example, dark or reddish urine, tachycardia, hyponatremia, muscle weakness, or use of medication known to exacerbate porphyria. Family history may be unrevealing because most carriers are asymptomatic.

The diagnosis is made by biochemical testing measuring porphyrines and its precursors. Urinary porphobilinogen levels are increased during the acute attack. In some cases of variegate porphyria and hereditary coproporphyria, the diagnosis might be missed since the elevation of urinary porphobilinogen is more transient.<sup>1,15</sup> Other quantitative tests are very informative (ALA and porphobilinogen) to determine the type of porphyria. The measurement of erythrocyte porphobilinogen deaminase activity and urine, plasma, and fecal porphyrin levels are also measured. The use of HPLC to measure coproporphyrines has great diagnostic importance.<sup>7</sup> It is recommended to measure enzyme activity to help to confirm the type of acute porphyria.<sup>3</sup> DNA studies can identify the disease-causing mutation or mutations. This then permits an accurate testing of asymptomatic family members. Most mutations are family-specific.<sup>3</sup> Patients with porphyria should have genetic counseling and should be encouraged to inform family members about the disease and its genetics so that they can make informed decisions about lifestyle and family planning.

Treatment consists of management of symptoms and complications. Hospitalization may be required to administer IV fluids, electrolytes, and glucose. Narcotic analgesic drugs are usually required. Carbohydrate loading provides nutritional replacement and is a standard treatment for acute

attacks. Tachycardia and hypertension may be treated cautiously with  $\beta$ -adrenergic blocking agents. Seizures can be controlled with gabapentin and phenothiazides. Benzodiazepines have proven to be well tolerated to treat seizures and insomnia. Hemin therapy consists in repressing hepatic ALA synthase activity, hence decreasing the overproduction of ALA and porphobilinogen.<sup>13,14,16</sup> Hemin is given IV 3-4 mg/kg per day for four days. It has been associated with improved outcome.<sup>1,13</sup> The most common side effect is phlebitis at the site of infusion, as well as fever, malaise, and hemolysis. Clinical improvement is rapid but, when the neuropathy is severe, complete recovery may take much longer.<sup>16</sup>

## DISCUSSION

We analyzed the case of a 47 year-old male with the diagnosis of porphyria. With the results, AIP was excluded since PBGD activity was normal. AIP is one the most frequent and severe types of acute porphyria. The differential diagnosis includes variegate porphyria but, since the patient did not present skin manifestations, the diagnosis could not be either confirmed or excluded. HCP is strongly considered in this case since the levels of coproporphyrines were markedly elevated. However, HCP is considered as a mild disease and recurrences are very rare, contrary to what was observed in our patient. It is 20 times less frequent than AIP. Sixty percent of the patients never manifest the disease and recurrences are very rare.<sup>5-7</sup>

This case is an important example of a not-so-rare disease that any physician should always have in mind when presented with a patient with unspecific clinical manifestations, with normal routine lab results and no relevant surgical findings. The diagnostic test is quite specific and is not done by routine, so it is important to consider porphyria in the differential diagnosis in order to make a prompt diagnosis and start appropriate treatment and management.

Patient education is important for the prevention of future attacks. Avoidance of alcohol, cigarette smoking, and drugs that can induce exacerbations and maintaining adequate nutrition are all very important. Medical alert bracelets are recommended to notify emergency medical personnel.<sup>5</sup>

There are still unknown exacerbating factors, modifier genes, and environmental and endogenous precipitating factors which is why it is an important research area. The molecular DNA test was not done. Empiric genetic counseling was provided to the patient. The standard treatment of acute porphyrias is intravenous Hemin, which has been approved by the FDA for over 30 years,<sup>1,16</sup> but unfortunately it is still not available in Mexico. So, in this case, the prevention of further attacks and patient education are of the utmost importance to maintain a good quality of

life. The administration of adenosine-5-monophosphoric acid (AMP), also known as adenylic acid, has proven to reduce the exacerbated synthesis of porphyrines and its precursors and can be used to control the acute attack.<sup>17,18</sup> Transplantation of hepatocytes and specific gene replacement therapy are also two possible future therapeutic strategies for patients with difficult control and frequent attacks.<sup>10</sup>

#### ACKNOWLEDGMENTS

The authors thank Laura Martínez de Villarreal, Chief of the Department of Genetics, UANL, and María del Carmen Esmer Sánchez, Research Coordinator of the Department of Genetics, UANL, for their critical reading of this manuscript.

#### REFERENCES

1. Anderson KE. Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med* 2005; 142:439-450.
2. Andersson C, Innala E, Backstrom T. Acute intermittent porphyria in women: clinical expression, use and experience of exogenous sex hormones. A population-based study in northern Sweden. *J Intern Med* 2003;254:176-183.
3. Scriver CR. Disorders of heme biosynthesis: X-linked sideroblastic anemia and the porphyrias. *Metabolic molecular bases of inherited disease*. McGraw-Hill; 2001.
4. Rimoin DL. Inherited porphyrias. *Emery and rimoin's principles and practice of medical genetics*. Elsevier; 2007.
5. Schuurmans MM, Xianoye Schneider-Yin, Schyder C, Minder C et al. Influence of age and gender on the clinical expression of acute intermittent porphyria Based on molecular study of porphobilinogen deaminase gene among Swiss patients. *Mol Med* 2001;7(8):535-542.
6. Gross U, Puy H, Meissauer U, Lamoril J, Deybach JC et al. A molecular, enzymatic and clinical study in a family with hereditary coproporphyria. *J Inherit Metab Dis* 2002;25:279-286.
7. Cacheux V, Martasek P, Fougereuse F, Delfau MH, Druart L et al. Localization of the human coproporphyrinogen oxidase gene to chromosome band 3q12. *Hum Genet* 1994;94:557-559.
8. González-Arriaza HL, Bostwick JM. Acute porphyrias: A case report and review. *Am J Psychiatry* 2003;160:450-459.
9. Brennan MJ, Cantrill RC. Delta-aminolaevulinic acid and amino acid neurotransmitters. *Mol Cell Biochem* 1981;(spec no):49-58.
10. Andersson C, Bjersing L, Lithner F. The epidemiology of hepatocellular carcinoma in patients with acute intermittent porphyria. *J Intern Med* 1996; 240: 195-201.
11. Kauppinen R, Von Und Zu Fraunberg M. Molecular and biochemical studies of acute intermittent porphyria in 196 patients and their families. *Clin Chem* 2002;48(11):1891-1900.
12. Andersson C, Wikberg A, Stegmayr B, Lithner F. Renal symptomatology in patients with acute intermittent porphyria. A population-based study. *J Intern Med* 2000;248:319-325.
13. Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Intern Med* 1993;153:2004-2008.
14. Jeans JB, Savik K, Gross CR, Weimer MK, Bossenmaier IC et al. Mortality in patients with acute intermittent porphyria requiring hospitalization: a United States case series. *Am J Med Genet* 1996;65:269-273.
15. Deacon AC, Peters TJ. Identification of acute porphyria: evaluation of a commercial screening test for urinary porphobilinogen. *Ann Clin Biochem* 1998;6:726-732.
16. Bonkowsky HL, Tschudy DP, Doherty J, Bossenmaier I, Cardinal R et al. Repression of the overproduction of porphyrin precursors in acute intermittent porphyria by intravenous infusions of hematin. *Proc Natl Acad Sci U S A* 1971;68(11):2725-2729.
17. Castellanos G, Anguiano G. Aspectos bioquímicos de la porfiria aguda intermitente. *Neurología-Neurocirugía-Psiquiatría* 1967;8(3):145-168.
18. Sardana MK, Padmanaban G. Effect of 2-Allyl-2-isopropylacetamide on poly(adenylic acid)-containing Ribonucleic Acid. *Biochem J* 1976;158:169-174.

Artículo sin conflicto de intereses

