Acute Hepatic Porphyrrias in Colombia: An Analysis of 101 Patients

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Abstract *Background:* There is minimal information available about acute hepatic porphyrias (AHPs) in developing countries. The aim of this study was to describe the demographics, clinical features, and mortality of AHPs in Colombia.

Patients and methods: 121 patients with presumed diagnosis of AHPs were reported in Colombia between 1944 and 2018. A pooled analysis of 53 patients with confirmed diagnosis was performed to evaluate the demographics, clinical features, and mortality of AHPs in the country. Selected variables were compared by periods (1952–2000 and 2001–2018).

Results: Most attacks occurred in women (66%), with a women-to-man ratio of 39/14. 96% of the patients were diagnosed with AHPs between 15 and 40 years of age. Precipitants were identified in 71% of attacks and more than one precipitant in 41% of them. Drugs (85%) and infections (44%) were the most common precipitants. 11% of women had premenstrual attacks. Abdominal pain was the most common symptom (96%). Cortical blindness, posterior reversible encephalopathy syndrome, and rhabdomyolysis were described. 70% of attacks were confirmed by qualitative test only. 67% of attacks were treated with

intravenous heme. The use of heme increased from 4 to 85% in the last two decades. Mortality decreased about twofold in relation to the increase in the use of heme. Severe motor neuropathy was associated with increased mortality. Gonadorelin analogues, heme prophylaxis, and orthotopic liver transplantation have been used to prevent recurrent attacks.

Conclusions: Diagnosis and treatment of AHPs in Colombia have improved in recent decades. However, there are still important shortcomings to address.

Abbreviations

AHPs	Acute hepatic porphyrias
AIP	Acute intermittent porphyria
ALA	Aminolevulinic acid
ALAS1	Aminolevulinic acid synthase 1
DNA	Deoxyribonucleic acid
GnA	Gonadorelin analogs
HCP	Hereditary coproporphyria
HMBS	Hydroxymethylbilane synthase
NAPOS	Norwegian Porphyria Centre
OLT	Orthotopic liver transplantation
PBG	Porphobilinogen
PRES	Posterior reversible encephalopathy syndrome
RNA	Ribonucleic acid
VP	Variegate porphyria

Introduction

Acute hepatic porphyrias (AHPs) are rare diseases caused by genetic mutations that lead to enzymatic deficiencies in the heme pathway. The most common AHPs are acute intermittent porphyria (AIP, OMIM 176000), hereditary coproporphyria (HCP, OMIM 121300), and variegate porphyria (VP, OMIM 176200).

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Clinical penetrance of mutations is low, so less than 10% of carriers develop acute attacks of neurovisceral manifestations. Attacks occur mainly in women of childbearing age and rarely before puberty. Symptoms and signs (e.g., abdominal pain, vomiting, hypertension, paresis, dysesthesia, and behavioral changes) are nonspecific and indistinguishable among AHPs and other more common diseases. These are precipitated by factors that induce aminolevulinic acid synthase 1 (ALAS1, EC.2.3.1.37) (e.g., hormones, drugs, infections, starvation, stress) (Bissell et al. 2017). Patients with HCP and VP may also develop blistering skin lesions either concurrently or in the absence of attacks.

Diagnosis of attacks is only possible by demonstrating elevated urinary porphobilinogen (PBG). A normal PBG excludes that concurrent symptoms are caused by AHPs (Woolf et al. 2017). Identification of individual porphyrias requires additional tests [analyses of porphyrins, hydroxymethylbilane synthase (HMBS, EC.2.5.1.61) enzymatic activity, or DNA] (Whatley et al. 2009).

Intravenous heme (Panhematin[®], Recordati Rare Diseases; Normosang[®], Orphan Europe) is the only specific treatment available for attacks. It must be administered to all patients with AHPs and severe attacks. Carbohydrate loading (oral or intravenous) is also a suitable therapy for mild symptoms (Stein et al. 2013).

A minority of patients develop severely debilitating recurrent attacks (≥ 4 attacks requiring hospitalization per year). Gonadorelin analogs (GnA) are administered to prevent premenstrual cyclic attacks. Heme is given prophylactically to prevent recurrent attacks unrelated to menstruation or refractory to GnA. Orthotopic liver transplantation (OLT) is an effective, but still experimental, treatment for patients who are disabled by frequent hospitalizations for attacks that are resistant to GnA or prophylactic heme (Balwani et al. 2017). There is minimal information available about AHPs in developing countries, such as Colombia. Clinical features and mortality of Colombian patients with symptomatic AHPs have been described only in case reports and small series from single centers. However, many patients in these studies were erroneously diagnosed, so results are inaccurate (Jaramillo-Calle 2017).

In this study, we reviewed 121 patients with presumed diagnosis of AHP who were reported in Colombia between 1944 and 2018. The demographics, clinical characteristics, diagnosis, treatment, and mortality of AHPs in the country were described.

Methods

Sources of information: PubMed, Scopus, Embase, Google Scholar, SciELO, and LILACS were searched using the terms “porphyria” and “Colombia” without restrictions (From inception to January 2018). Case reports and series

describing patients with AHPs were evaluated if the primary author affiliation was in Colombia. References of selected articles were checked manually to identify unrecovered studies.

Patients: 121 patients with presumed AHPs were reported in Colombia between 1944 and 2018 (full list of references in Supplementary Material). Five reports were excluded for duplication and one for being about a cutaneous porphyria. 115 reports were reviewed, of which 14 (12%) were excluded due to unconfirmed diagnosis of AHPs. At the end, we included 101 patients with confirmed AHPs. For each patient, there was information available about a single attack.

Definitions: Confirmed diagnosis of AHPs was defined as (1) compatible symptoms of attacks and elevated PBG (qualitatively or quantitatively) or (2) confirmatory tests to identify the type of porphyria (analyses of porphyrins, HMBS enzymatic activity, or DNA) (Whatley et al. 2009). Porphyrinogenic risk of medications was evaluated in the NAPOS drug database (www.drugs-porphyria.org) (complete list in Supplementary Material). Attacks were defined as severe if any of the following manifestations occurred: paresis, bulbar palsy, respiratory failure, hyponatremia, seizures, psychosis, or lethargy (Stein et al. 2013; Pischik et al. 2004).

Statistical analysis: A pooled analysis of 53 patients with individual information available was performed to evaluate demographics, clinical features, diagnosis, treatments, and outcomes of attacks. Descriptive statistics were generated. In the analysis of each variable, only patients with information available were considered. Mortality of attacks was calculated as the number of patients who died during the reported attack divided by the total number of patients. Analyses of attacks severity, diagnosis, treatment, and mortality were stratified by periods (1952–2000 and 2001–2018) to assess changes. Comparisons were performed by Wilcoxon rank sum test for continuous variables and Fischer’s exact test for categorical variables. Two-sided p values < 0.05 indicated statistically significant differences. Analyses were performed using Stata Software v.14.2.

Results

Geographical distribution: Fig. 1 presents the geographic distribution of 101 Colombian patients with AHPs by place of birth and diagnosis. As expected, most patients were identified in densely populated capital cities with the greatest access to tertiary-level medical centers (Medellín, Bogotá, Cali).

Sex and age: Most attacks occurred in women (66%), with a women-to-man ratio of 39/14. Median age at diagnosis was 26 years [women, 27 years (15–50) vs.

Fig. 1 Places of birth and diagnosis of patients with acute hepatic porphyrias in Colombia. This figure shows that most patients were born ($n = 27$, triangles) or diagnosed ($n = 74$, circles) in the central

region of the country (black oval), with predominance in the three largest and densely populated capitals of Colombia (Medellín, Bogotá y Cali)

men, 25 years (15–42), $p = 0.24$]. 51 (96%) patients were diagnosed with AHPs between 15 and 40 years of age.

Precipitants: Precipitants were identified in 71% of attacks (>1 precipitant in 41%) (Fig. 2). The most common precipitants were drugs (85%) and infections (44%). 11% of women had premenstrual attacks. Eight pregnancies occurred and were complicated by attacks during or soon after pregnancy in three instances. One woman with four pregnancies had a mild attack probably due to the use of a porphyrinogenic compound (*laudanum*: Alcohol and opium

tincture) (Ramírez 1959); another woman with two pregnancies had two attacks in which precipitants were not identified (Contreras-Zúñiga and Zuluaga-Martínez 2006); another woman with one pregnancy had one attack due to a postpartum endometritis (Mendoza et al. 1995); and another woman with one pregnancy had no attacks (Argüello et al. 1978).

Clinical manifestations: 85% of attacks were severe. Severity was not significantly different between periods (1952–2000, 81% vs. 2001–2018, 93%; $p = 0.4$) or sexes

Fig. 2 Frequency of precipitant factors of 53 attacks in 53 patients with acute hepatic porphyrias in Colombia

(women, 88% vs. men, 80%; $p = 0.6$). 96% of patients had abdominal pain alone or in combination with other manifestations (Table 1). Three women presented posterior reversible encephalopathy syndrome (PRES) (Adams and Amaya 2014; Uribe et al. 2007; Enriquez-marulanda et al. 2016), and one of them had also acute rhabdomyolysis (Adams and Amaya 2014).

Diagnosis: In 96% of patients, diagnosis of AHPs was confirmed by elevated PBG. Quantitative PBG tests were used in 30% of attacks, increasing from 24% before 2001 to 42% afterward. In one patient, diagnosis of AHPs was confirmed by DNA analysis, in which a HMBS gene mutation (c.1084delT) compatible with AIP was identified (Angel et al. 2010). Of the patients confirmed to have AHPs, 98% were diagnosed with AIP based exclusively on clinical manifestations and an elevated PBG, without further testing to differentiate whether they might have HCP or VP instead of AIP.

Treatment: The use of heme in Colombia was reported for the first time in 1980 (Pradilla et al. 1980). Since then, 67% of attacks were treated with heme. The use of heme increased from 4% of attacks before 2000 to 85% afterward ($p < 0.001$). 18% of attacks were treated with carbohydrates loading (oral or intravenously) and heme, 21% with carbohydrates loading only, and 47% with symptomatic measures only (e.g., analgesics, antispasmodics, anticonvulsants, antiemetics, among others). Median hospital stay length was 21 days (7–70 days).

Prevention: 55% of the patients reported a history of multiple episodes of compatible symptoms of attacks before the diagnosis of AHPs was confirmed, being this more frequent among women (75% vs. 69%). One woman suffered severely debilitating premenstrual cyclic attacks, with more than 14 attacks per year on average. Despite receiving GnA and heme prophylaxis, she continued to present recurrent attacks and additionally developed serious side effects. OLT was performed with the subsequent disappearance of symptoms and normalization of urinary ALA and PBG (Jaramillo-Calle et al. 2018).

Mortality: Mortality of attacks during the period covered by the study was 32%. It was 38% between 1952 and 2000, with minimal changes within the period (1952–1979, 38%; 1980–2000, 40%), and decreased to 14% between 2001 and 2018. Patients who did not receive heme died approximately twofold more frequently than patients treated with heme (31% vs. 17%). Two patients died among those who received heme (80% success rate). The most common cause of death was respiratory paralysis with severe pulmonary sepsis (85%). Median age at diagnosis did not differ significantly between patients who survived and those who died [survivors, 27 years (16–50) vs. dead, 24 years (17–43) $p = 0.8$]. Patients who died developed severe motor neuropathy more frequently than patients who survived [paresis (36% vs. 0%; $p = 0.04$), quadriplegia (42% vs. 0%; $p = 0.007$), bulbar palsy (48% vs. 0%; $p = 0.001$), respiratory failure (53% vs. 4%; $p = 0.0004$)]. There were no significant differences in other severe manifestations [hyponatremia (20% vs. 27%; $p = 0.7$), seizures (9% vs. 31%; $p = 0.2$), and consciousness impairment (50% vs. 21%; $p = 0.12$)].

Discussion

Sex and age: Attacks occurred more often in women (66%) and exclusively at age 15 or later, which makes it unlikely prepubertal. This predominance of attacks in women and fertile ages is attributed in part to the effect of sex hormones, which are important precipitants of attacks and increase substantially during puberty (Andersson et al. 2003).

Menstruation and pregnancy: 11% of women in this study had premenstrual attacks, which are attributed in part to an increase in progesterone during the luteal phase of the menstrual cycle. Pregnancy theoretically raises the risk of attacks, since estrogen and progesterone levels increase prominently. Four of the women in this study had a total of eight pregnancies; three of these women had attacks during a pregnancy each. Nevertheless, only the attacks in one woman were precipitated by pregnancy while the attacks in the other two women were precipitated by a porphyrinogenic compound and an infection. This supports that, despite the higher concentrations of hormones, most pregnancies in women with AHPs are not complicated by attacks. When attacks occur during pregnancy, they are mainly due to exposure to typical precipitants (Marsden and Rees 2010; Kauppinen and Mustajoki 1992).

Clinical manifestations: Almost all patients had abdominal pain, as in most studies. Paralysis and respiratory failure were more common in this study than other studies (Table 1). Hypertension was the most frequent clinical sign instead of

Table 1 Clinical manifestations of patients with symptomatic acute hepatic porphyrias in different studies

Signs and symptoms (%)	Current	A	B	C	D	E	F	G	Median	(min–max)
Abdominal pain	96	95	95	100	97 ^a	86	74	93	95	(74–100)
Paralysis/quadruparesis	60	31	–	59	–	–	–	26	45	(26–60)
Psychiatric ^b	49	40	25	18	1	29	55	40	34.5	(1–55)
Dark urine	47	74	90	–	–	–	–	64	69	(47–90)
Respiratory failure	45	7	20	–	–	–	–	–	20	(7–45)
Constipation	40	48	80	37	27	41	60	46	43.5	(27–80)
Hypertension	38	36 ^c	55 ^d	–	74 ^e	–	40	–	40	(36–74)
Palpitations/tachycardia	32	80	85	30	37	10	50	53	43.5	(10–85)
Nauseas/vomiting	30	43	80	11	79	36	73	47	45	(11–80)
Sensory impairment	28	26	25	–	–	7	–	39	26	(7–39)
Seizures	26	20	20	30	–	1	9	–	20	(1–30)
Myalgia	17	50 ^f	70	–	–	30	–	63	50	(17–70)
Muscle paresis/weakness	10	29	50	48	–	20	63	59	48	(10–63)
Diarrhea	8	5	5	–	–	–	29	–	6.5	(5–29)
Fatigue	–	–	–	–	–	42	–	72	57	(42–72)
Headache	–	5	–	–	–	13	–	52	13	(5–52)
Fever	–	9	–	–	–	–	18	–	13.5	(9–18)
Anorexia	–	–	–	37	–	–	–	–	37	–

A Stein and Tschudy (1970), B Mustajoki and Koskelo (1976), C De Siervi et al. (1999), D Hift and Meissner (2005), E Bylesjö et al. (2009), F Bonkovsky et al. (2014), G Mykletun et al. (2014)

^a Any pain

^b Including anxiety, depression, behavioral changes, hallucinations, confusion

^c Diastolic >90

^d Diastolic ≥100

^e Systolic >130

^f Pain or paresthesia

tachycardia. PRES occurred in three women (Adams and Amaya 2014; Uribe et al. 2007; Enríquez-marulanda et al. 2016). Numerous reports of PRES during an attack have emerged in recent years with the increased availability of neuroimaging in the emergency department. One patient had cortical blindness, which has been previously reported (Kupferschmidt et al. 1995; Garg et al. 1999; Bhat et al. 2010). Severe acute rhabdomyolysis occurred in an Afro-American woman with hyponatremia and hypokalemia (Adams and Amaya 2014). Other five patients with rhabdomyolysis during an attack have been reported in the literature (Marsden and Peters 2004; García-Martul et al. 2008; Yrjönen et al. 2008; Chen et al. 2015; Devars du Mayne et al. 1987). Potential pathophysiological mechanisms for these manifestations during an attack are discussed elsewhere (García-Martul et al. 2008; Olivier et al. 2017).

Diagnosis: Of the 115 symptomatic patients with presumptive diagnosis of AHPs, 14 (12%) were excluded because there was no evidence to support the diagnosis. Of these 14 patients, one had liver disease, and the diagnosis of AHP was based only on elevated porphyrins in urine

without having measured the PBG (Ordoñez 1944), which could have been explained by a secondary porphyrinuria due to hepatic dysfunction (Doss 1987). Another patient had elevated urinary aminolevulinic acid (ALA) and normal PBG (Mendoza et al. 1995), which can occur in ALA dehydratase porphyria, lead poisoning, and type 1 hereditary tyrosinemia. The remaining 12 patients had normal or unmeasured PBG despite being symptomatic, and no other evidence (i.e., personal or family history or other porphyria tests) was informed to support the diagnosis of AHPs (Latorre and Muñoz 1988). These findings suggest that many subjects diagnosed with AHPs in Colombia might not really have these diseases. The diagnosis of AIP in 98% of the patients confirmed to have AHPs was based exclusively on clinical manifestations and elevated PBG, without further testing to differentiate whether they might have HCP or VP instead of AIP. These patients should have been diagnosed with unspecified AHP. In only one patient, AIP was diagnosed by analysis of the HMBS gene in which a small deletion mutation was found (c.1084delT). This patient had previously presented symptoms compatible

with an attack, but measurements of urinary PBG were not available (Angel et al. 2010). The same mutation was identified in a 16-year-old female with a confirmed attack in the USA (Leung-Pineda and Wilson 2017). The mutation changes a stop codon and produced a mutant HMBS protein longer than the normal enzyme, which is predicted to result in no-go decay (Chen et al. 2018). Finally, 70% of attacks were evaluated using qualitative test only (i.e., Watson-Schwartz or Hoesch tests), which experts no longer recommend due to the high risk of false results (Woolf et al. 2017; Balwani et al. 2017; Deacon 2011). This is probably explained by the higher cost and lower availability of quantitative test. The previously mentioned findings suggest important limitations in availability, use, and interpretation of diagnostic tests to confirm the attacks and identify the types of AHPs in Colombia.

Treatment and prognosis: Mortality of attacks decreased from 38 to 14% in relation to increase in the use of intravenous heme, supporting that the prognosis of attacks has improved since the introduction of heme therapy (Jeans et al. 1996; Kauppinen and Mustajoki 1992). Two patients treated with heme died in this study, probably because the delayed administration of the drug (20 and 24 days after admission) (Pradilla et al. 1980; Buitrago and Santa 2009). Heme is more effective when administered early, since it cannot reverse established nerve damage (Mustajoki and Nordmann 1993). In addition to heme therapy, overall improvement in the quality of life and healthcare in Colombia during the last decades is likely to have contributed to the decrease in mortality of attacks, especially the greater availability of intensive care units and mechanical ventilatory support. Mortality was significantly higher among patients who developed severe motor neuropathy (i.e., paresis, quadriplegia, or respiratory failure), which occurs in very advanced and untreated attacks. This supports that these clinical manifestations predict a poor prognosis in attacks (Pischik et al. 2004).

Prevention of recurrence: A woman with AIP and severe premenstrual cyclic attacks received GnA to suppress menstruation, but the attacks continued to recur (Jaramillo-Calle et al. 2018). Studies have shown that the effectiveness of GnA in ameliorating attacks related to menstruation varies among women; although most women can perceive a complete or partial improvement, some few do not experience any change (Schulenburg-Brand et al. 2017; Innala et al. 2010). It is possible that, in addition to the hormonal changes, other unrecognized precipitants contribute to the attacks of these women. Also, some unknown genetic factor related to the severity and frequency of attacks might modulate the response to GnA. Monthly heme infusions were also given prophylactically to this patient, but they were ineffective to stop the recurrent attacks. This is consistent with studies showing that most

patients receiving heme prophylaxis continue having acute and chronic symptoms (Sardh et al. 2017; Marsden et al. 2015). A recent study has shown that frequent administration of heme infusions can lead to a chronic inflammation of the liver that induces heme oxygenase-1, increases the degradation of heme, and preserves the overexpression of ALAS1, situation that might perpetuate and aggravate the recurrence of long-term attacks (Schmitt et al. 2018). The patient developed severe side effects due to chronic use of heme (i.e., anaphylaxis and iron overload). It has been shown that a long-term iron overload due to prolonged use of heme can be associated with liver fibrosis (Willandt et al. 2015). She underwent OLT, which produced complete clinical and biochemical remission of AIP by correcting the genetic mutation in the liver (Soonawalla et al. 2004). This was the first time this procedure was reported in Latin America (Jaramillo-Calle et al. 2018).

New drugs for prevention and treatment of attacks are currently under evaluation. A gene therapy to transport the normal HMBS gene to hepatocytes showed promising results in preclinical studies (Yasuda et al. 2010) but failed to reduce ALA and PBG levels in humans (D'Avola et al. 2016). Another therapy is a small interfering RNA against ALAS1 (Givosiran, Alnylam Pharmaceuticals) that demonstrated efficacy in reducing circulating ALAS1-mRNA and urinary ALA and PBG in humans (Sardh et al. 2016). A phase III study of Givosiran is currently underway ([ClinicalTrials.gov: NCT03338816](https://clinicaltrials.gov/ct2/show/study/NCT03338816)).

One limitation of this study is that case reports and series are written retrospectively from medical records, so all relevant information may not have been included. Furthermore, case reports usually present severe or unusual forms of a diseases, which could explain the high frequency of severe symptoms in this study. Despite these limitations, this is the most extensive description of AHPs in Colombia to date and provides a ground for future research.

Conclusions

During 65 years, there have been important deficiencies in availability, use, and interpretations of porphyria diagnostic tests in Colombia. Our study suggests that 12% of patients considered as having AHPs are erroneously diagnosed because the necessary tests are not performed or their results are not interpreted properly, less than 50% of attacks are confirmed by quantitative PBG tests, diagnostic tests to identify the types of porphyrias are performed in less than 2% of patients with confirmed diagnosis of AHPs, and genotype of AHPs is almost unknown. In view of these diagnostic problems, it is very likely that AHPs are widely underdiagnosed in the country. These issues will be solved through the establishment of specialized porphyria laboratories that participate in external quality assurance

schemes (Aarsand et al. 2011). On the other hand, the use of heme in Colombia has increased greatly in the last two decades. Consequently, mortality has decreased more than twofold. Finally, delayed diagnosis, severe motor neuropathy, and late administration of heme are associated with a poor prognosis. Therefore, efforts in Colombia should be directed toward making PBG tests and intravenous heme available within 24 h for symptomatic patients with known or suspected diagnosis of AHPs and attacks.

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Compliance with Ethics Guidelines

Conflict of Interest

Daniel A. Jaramillo-Calle and Daniel C. Aguirre Acevedo declare that they have no conflict of interest.

Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Details of the Contributions of Individual Authors

Daniel A. Jaramillo-Calle designed the study, analyzed and interpreted the data, and drafted and reviewed the article. He is guarantor for the article.

Daniel C. Aguirre Acevedo participated in the design of the study and had input for revising the article.

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