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ORIGINAL ARTICLE

PICO questions and DELPHI methodology for improving the management of patients with acute hepatic porphyria

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KEYWORDS
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Abstract
Background: Acute hepatic porphyrias (AHPs) are a group of rare diseases that encompasses acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and

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Acute hepatic porphyria;
DELPHI methodology;
PICO questions

5-aminolaevulinic acid dehydratase deficiency porphyria. Symptoms of AHP are nonspecific which, together with its low prevalence, difficult the diagnosis and follow-up of these patients.
Material and methods: This project used DELPHI methodology to answer PICO questions related to management of patients with AHPs. The objective was to reach a consensus among multidisciplinary porhyria experts providing answers to those PICO questions for improving diagnosis and follow-up of patients with AHP.
Results: Ten PICO questions were defined and grouped in four domains: 1. Biochemical diagnosis of patients with AHP. 2. Molecular tests for patients with AHP. 3. Follow-up of patients with AHP. 4. Screening for long-term complications of patients with AHP.
Conclusions: PICO questions and DELPHI methodology have provided a consensus on relevant and controversial issues for improving the management of patients with AHP.

PALABRAS CLAVE
Enfermedades minoritarias;
Porfiria;
Porfiria hepática aguda;
Metodología DELPHI;
Preguntas PICO

Preguntas PICO y metodología DELPHI para mejorar el manejo de los pacientes con porfiria hepática aguda

Resumen
Antecedentes: Las porfirias hepáticas agudas (PHA) son un grupo de enfermedades minoritarias que incluyen la porfiria aguda intermitente, la porfiria variegata, la coproporfiria hereditaria y la porfiria por deficiencia de la 5-aminolevulínico ácido deshidratasa. Los síntomas de la PHA son inespecíficos, lo que, junto a su baja prevalencia, hacen que el diagnóstico y seguimiento de estos pacientes sea complejo.
Materiales y métodos: Este proyecto utilizó la metodología DELPHI para responder unas preguntas PICO relacionadas con el manejo de pacientes con PHA. El objetivo fue alcanzar un consenso multidisciplinario entre expertos en porfiria sobre esas preguntas PICO para mejorar el diagnóstico y seguimiento de los pacientes con PHA.
Resultados: Se definieron diez preguntas PICO y se agruparon en cuatro dominios: 1. Diagnóstico bioquímico de los pacientes con PHA. 2. Estudio molecular de los pacientes con PHA. 3. Seguimiento de los pacientes con PHA. 4. Cribado de complicaciones a largo plazo en los pacientes con PHA.
Conclusiones: Las preguntas PICO y la metodología DELPHI han proporcionado un consenso sobre temas relevantes y controvertidos para mejorar el manejo de pacientes con PHA.

Introduction

Heme is the non-amino acid component of different proteins essential to carry out a wide range of vital functions, such as hemoglobin, catalases or peroxidases. Heme is synthesized through eight enzymatic steps, and pathogenic variants or mutations in the genes that encode these enzymes give rise to the eight subtypes of porphyria.[1,2] Acute hepatic porphyrias (AHP) are a subgroup of minority diseases (ORPHA: 95157) that include acute intermittent porphyria (AIP) (the most common), variegate porphyria (PV), hereditary coproporphyria (CPH) and the extremely rare, porphyria due to delta-aminolevulinic acid (ALA) dehydratase deficiency (ADP).[3,4] PV and CPH are mixed porphyrias, which also present skin involvement.[1–4] In patients with AHP, upon exposure to precipitating factors, the decrease in the heme group due to the enzymatic blockade causes the induction of hepatic ALA synthase 1 (ALAS1), which, together with the enzymatic blockade that the patient presents due to his disease, results in the accumulation of ALA and porphobilinogen (PBG), the so-called porphyrin precursors. These precursors cause damage to the nervous system and other organs, causing acute, life-threatening attacks and chronic manifestations of the disease.[2,4]

Although suggestive, the symptoms of AHP are nonspecific and vary widely in severity. Therefore, the detection of high levels of ALA and PBG in urine are key findings for the diagnosis of an acute attack.[2] The Hoesch test can detect the presence of PBG in urine quickly, becoming an excellent qualitative test in the screening of a possible porphyria attack. In this test, two drops of fresh urine are added to 1 mL of Ehrlich's reagent (solution containing the PBG indicator p-dimethylaminobenzaldehyde dissolved in hydrochloric acid). In case of an increase in PBG in the urine sample, upon contact with the indicator, a cherry red color immediately develops throughout the tube after shaking.[5,6] Porphyrin precursors should be determined and quantified specifically in urine after the Hoesch test to confirm the diagnosis. For this, a 24-h urine sample is not necessary, but a simultaneous urine sample must be used and the ALA and PBG

concentrations must be corrected to avoid dilution biases, by correlating them with the creatinine concentration in the sample obtained.[5,7]

The symptoms and clinical course of AHP are highly variable, making the diagnosis and follow-up of these patients difficult. In fact, Waldenström described acute porphyria as the little imitator in 1937, contrasting it with syphilis, the great imitator of the early 20th century.[8] In this sense, our study aims to seek a consensus among porphyria experts to improve the diagnosis and follow-up of patients with AHP.

Materials and methods

Study design

This is a multicenter and multidisciplinary work between experts in the management of patients with AHP. The duration of the project was 6 months, from June to December 2023. The study was approved by the Clinical Research Ethics Committee of the Hospital Universitari de Bellvitge (Barcelona, Spain; approval number PR280/23).

The main objective was to reach a consensus on the prevention, diagnosis and follow-up of patients with AHP in different controversial clinical scenarios, excluding pharmacological treatment.

The methodology established a set of clinical problems through PICO questions (Patient, Intervention, Comparison, Outcomes) and then the DELPHI method was applied to prepare the answers.[9–11] DELPHI is a structured methodology that systematically collects expert opinions on a specific problem and allows a group consensus to be built.[10,11] The key characteristic that allows consensus to be reached is that participants receive feedback on their answers and can adjust and agree on them through an iterative process.[10,11] The benefits of the combination of PICO questions and the DELPHI methodology have been widely described in previous studies.[9–12]

A Scientific Committee (AR-M, EG-N and MM-C) recruited a panel of six experts (JSGM, JCF, MEH-C, PAP, JJ and FMV) in the management of patients with porphyria from different centers in Spain. The project was developed in four phases. In phase 1, the domains and PICO questions were defined. In phase 2, the PICO questions were discussed and answered in three recorded rounds. In phase 3, through several rounds of feedback with all experts, a global response was drafted for each PICO question. The expert panel used the terms ''recommended'' or ''suggested'' depending on whether the strength of the recommendation was strong or weak, according to the degree to which one can be confident that the desirable effects of an intervention exceed to its undesirable effects.[13] Finally, in phase 4, each panel member individually assessed whether they agreed, disagreed, or neither agreed nor disagreed with the answers to the PICO questions, and the degree of consensus was compiled according to the absolute frequencies of said assessment.

Terminology used

The panel used some key terms and definitions recently established by the European Porphyria Network (EPN) for terms related to the diagnosis, treatment and follow-up of patients with PHA.[7] These definitions of the typical patterns of porphyria according to symptoms and the excretion of precursors in urine are shown in Fig. 1. In addition, the definition of acute porphyria attack was adopted as an episode that includes $\geq$ 2 of the following manifestations: intense pain (mainly in the abdomen), nausea, vomiting, constipation, urinary retention or incontinence, systemic arterial hypertension, tachycardia, hyponatremia, peripheral neuropathy, or central nervous system involvement (e.g., seizures, psychosis, or posterior reversible encephalopathy syndrome), typically persisting for more than 24 h in the absence of other probable explanations, together with elevation of precursors (ALA and PBG) in urine. An acute porphyria attack was defined as severe if it was associated with $\geq$ 1 of the following characteristics: urinary retention or incontinence, significant hyponatremia, arrhythmias, peripheral neuropathy, or central nervous system involvement. The panel referred to a compatible biochemical phenotype as one that includes the elevation of porphyrin precursors (ALA and PBG) in urine and porphyrins, both in urine and feces (in the latter case, in mixed porphyrias, PV and CPH). This complete biochemical phenotype allows biochemical diagnosis to be made between the different subtypes of porphyria.

Results

PICO questions were defined divided into four domains (Table 1).

Domain 1: biochemical diagnosis of patients with AHP

PICO 1. In which patients treated in the Emergency Department for abdominal pain should we perform the Hoesch test?

1. In those patients with a history of recurrent abdominal pain or even if it is the first episode, with intense or severe pain (for example, with hyponatremia or neurological involvement), it is recommended to perform the Hoesch test as part of the initial etiological study.
2. It is suggested to perform the Hoesch test in young adults (15—50 years) seen in the emergency room for abdominal pain, without a specific diagnosis after having carried out a reasonable etiological study.

Consensus: 9/9 in agreement

Comments: The simplicity of the Hoesch test makes it a valuable tool in Emergency settings where a rapid diagnosis is essential to initiate adequate treatment.[5,6] Abdominal pain is the most common symptom of an acute attack and is usually severe, generalized and accompanied by nausea, vomiting, constipation or diarrhea.[14] AHP should be considered in the differential diagnosis of abdominal pain, especially when an initial diagnostic evaluation does not suggest a more common cause, even in male patients. After a positive Hoesch test result, quantitative determination of the compatible biochemical phenotype is essential to confirm the diagnosis and identify the porphyria subtype.[5–7]

Table 1 Domains with their respective PICO questions.

Domain	PICO questions
Domain 1: Biochemical diagnosis of patients with AHP	**PICO 1. In which patients treated in the Emergency Department for abdominal pain should we perform the Hoesch test?** P: Young adult patients (15—50 y/o) treated in the Emergency Department for abdominal pain. I: Perform the Hoesch test C: Do not do it O: Diagnosis of AHP **PICO 2. In the differential diagnosis of acute/subacute progressive sensory-motor axonal neuropathy, should we include AHP and what initial test should we perform?** P: Patients with atypical neuropathy type Guillain-Barré syndrome I: Perform the Hoesch test and determination of porphyrin precursors in urine C: Do not do it O: Diagnosis of AHP **PICO 3. What should be the next diagnostic step in those patients with suspected AHP and a negative Hoesch test?** P: Patient with clinical suspicion of PHA and a negative Hoesch test I: Perform a quantitative biochemical study of precursors in urine C: Do not do it O: Diagnosis of AHP
Domain 2: Molecular study of patients with AHP	**PICO 4. What complementary study should be performed in patients with a clinical and biochemical phenotype compatible with AHP?** P: Patient with clinical suspicion of PAH and compatible biochemical profile I: Perform genetic study of the associated genes (HMBS, CPOX, PPOX and ALAD) using massive sequencing (panel/clinical exome) or Sanger C: Do not do it O: Confirmation of AHP **PICO 5. What studies should we perform in patients with a clinical-biochemical profile compatible with AHP and massive sequencing of the associated genes that is negative or inconclusive?** P: Patient with symptoms and alteration of biochemical parameters compatible with PAH and negative or inconclusive genetic study I: Carry out other genetic studies according to a biochemical pattern, in a genetics reference center C: Do not do it O: Genetic diagnosis of AHP **PICO 6. What type of first-line complementary test should be performed in the relatives of a patient with genetically characterized AHP?** P: Asymptomatic relatives of an index patient diagnosed with AHP I: Perform genetic study of the familial variant associated with AHP C: Do not do it O: Diagnosis of AHP in asymptomatic patients
Domain 3: Follow-up of patients with AHP	**PICO 7. Should monitoring that includes determination of porphyrin precursors in the urine of patients with AHP be performed?** P: Symptomatic and asymptomatic AHP patients I: Perform biochemical monitoring of porphyrin precursors in urine periodically C: Carry out clinical follow-up exclusively O: Assess the degree of AHP activity **PICO 8. Is a positive Hoesch test always diagnostic of an acute attack in a patient with AHP who consults for abdominal pain?** P: Patients with a diagnosis of AHP and suspected acute attack I: Rely exclusively on the Hoesch test C: Compare the levels of porphyrin precursors (ALA/PBG) in urine at that time with their baseline and note a significant increase. O: Diagnosis/exclusion when acute attack is suspected
Domain 4: Screening for long-term complications in patients with AHP	**PICO 9. Should patients with PHA be screened for hepatocellular carcinoma (HCC)?** P: Patients with AHP, symptomatic and asymptomatic I: Perform periodic ultrasound (every 6—12 months)

Table 1 (*Continued*)

Domain	PICO questions
	C: Do not do it O: Early diagnosis of HCC **PICO 10: Should periodic monitoring of blood pressure (BP) and kidney function be performed in patients with AHP?** P: Symptomatic and asymptomatic AHP patients I: Perform periodic (annual) monitoring of BP levels and kidney function (creatinine and glomerular filtration rate) C: Not making such periodic determinations O: Early diagnosis and treatment of high blood pressure or kidney failure

Abbreviations: PICO: Patient, Intervention, Comparison, Outcomes; AHP: acute hepatic porphyria.

PICO 2. In the differential diagnosis of acute/subacute progressive sensory-motor axonal neuropathy, should we include AHP and what initial test should we perform?

1. In patients with acute/subacute progressive Guillain-Barré type sensory-motor axonal neuropathy with atypical characteristics, it is recommended to perform the Hoesch test to accelerate the diagnosis and be able to administer the appropriate treatment.
2. If there is a high clinical suspicion, it is recommended to simultaneously request a quantitative study of precursors (ALA and PBG) in urine, even if the result of the Hoesch test is negative.

Consensus: 9/9 in agreement

Comments: Peripheral neuropathy in AHP can be motor, sensory or mixed, and symptoms are highly variable, including pain in the extremities, muscle weakness or loss of sensation. Although rare, AHP can also manifest as acute progressive ascending paralysis, simulating Guillain-Barré syndrome.[15,16] The onset may be symmetrical or asymmetrical and affect the arms or legs proximally. This condition can progress to quadriplegia and respiratory failure, requiring admission to an Intensive Care Unit.[15,16]

It is important to note that AHP is treatable and, therefore, potential disability can be prevented if the neuropathy is diagnosed and treated early. There may be signs of suspected AHP as the cause of neurological symptoms, such as a recent history of abdominal pain, hyponatremia, or known precipitating factors.[2,17] The Hoesch test can be an initial and efficient tool in the diagnostic process.[5,6]

PICO 3. What should be the next diagnostic step in those patients with suspected AHP and a negative Hoesch test?

1. If a high clinical suspicion persists, it is recommended to quantify the urinary excretion of porphyrin precursors (ALA and PBG) before ruling out an acute porphyria attack.

Consensus: 9/9 in agreement

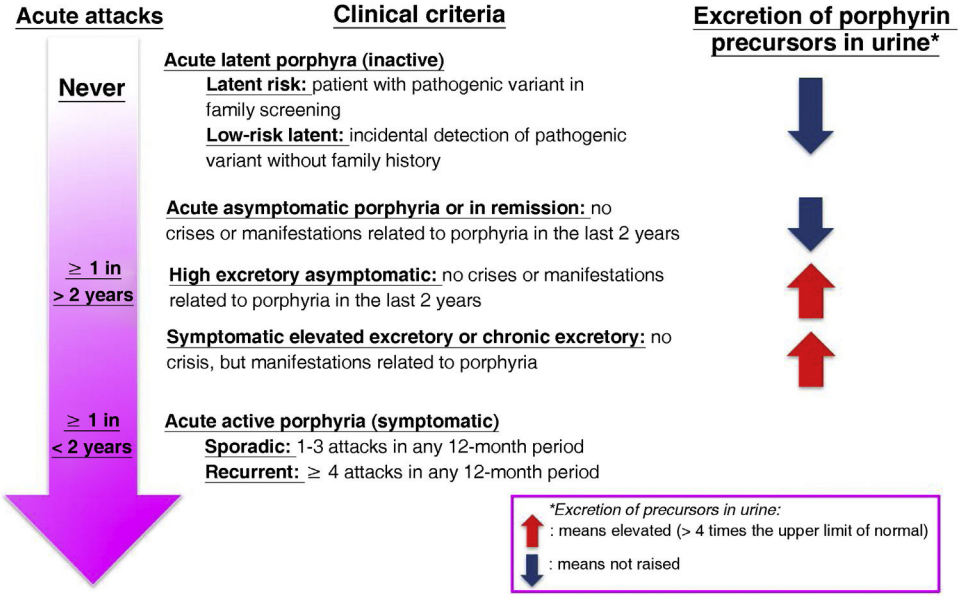

Figure 1 Typical patterns of porphyria according to symptoms and excretion of precursors in urine.

Comments: In patients with a high clinical suspicion, additional tests are needed to confirm the diagnosis and type of porphyria, even if the Hoesch test result is negative.[5–7] In fact, small increases in PBG may go unnoticed when using this test. Despite this, it is a very unusual situation in patients with an acute attack, since they present markedly elevated levels of PBG in urine (in the range of 10–20 times higher).[5,6] Other possible false negatives of the Hoesch test include technical problems, although they are very rare in this simple test.[5] It must also be considered that the Hoesch test is negative in ADP and also in hereditary tyrosinemia type I and in some entities with symptoms superimposable to AHP, such as lead poisoning, where only elevation of ALA occurs.[5,14,18]

Despite these rare situations, the reliability of the test depends on the clinical scenario. If there is severe abdominal pain, a negative result should point to causes other than AHP. However, in young women, a negative result should be confirmed with the quantification of urinary precursor excretion before porphyria is ruled out.[2,4,5,7]

Domain 2: Molecular study of patients with AHP

PICO 4. What complementary study should be performed in patients with a clinical and biochemical phenotype compatible with AHP?

1. In these patients, it is recommended to perform a molecular study through massive sequencing (specific panel or clinical exome).
2 If the patient comes from an area in which there is a pathogenic genetic variant with a founder effect associated with AHP, the direct study of said variant using Sanger sequencing can be cost-effective.

Consensus: 9/9 in agreement

Comments: In patients with a biochemical phenotype compatible with AHP, diagnostic confirmation is established by genetic study. Carrying out this study without knowing the clinical-biochemical profile may lead to problems in interpreting the identified genetic variants.[4] In patients without studied family history, massive sequencing (NGS) is recommended, which includes at least the four genes associated with AHP (HMBS, CPOX, PPOX and ALAD), using a specific panel or clinical exome. With this study, between 95–99% of porphyria cases are molecularly characterized.[18,19] The gene most frequently implicated is the HMBS gene, related to AIP. The current penetrance of this disorder is unknown, but it is estimated to be around 1% in asymptomatic carriers, and greater than 20% in those families with patients who manifest the disease.[20,21] In the initial study of patients from areas with an identified founder effect, the direct study of the pathogenic variant using Sanger sequencing is currently cost-effective.[19–22] Likewise, it is indicated to perform genetic counseling before and after performing the genetic test.

PICO 5. What studies should we perform in patients with a clinical-biochemical profile compatible with AHP and massive sequencing of the associated genes that is negative or inconclusive?

1. If the clinical and biochemical profile is compatible with AHP and its genetic basis has not been identified by massive sequencing, it is recommended to refer to a genetics center with expert personnel in AHP for an advanced study.

Consensus: 9/9 in agreement

Comments: The assumption that it exists clinical and biochemical evidence of AHP and that sequencing is negative or inconclusive is very rare (<5%).[19] If the clinical-biochemical suspicion persists, other genetic studies should be performed, such as multiplex ligation dependent probe amplification (MLPA) to rule out deletions/duplications, long-read sequencing to screen for structural alterations, array comparative genomic hybridization (aCGH), functional tests for variants of uncertain clinical significance or specific enzymatic studies, which allow identifying their molecular basis.[23] For this, it is necessary to refer the samples to a genetics center with expert personnel in AHP, for the complete characterization of these patients.

PICO 6. What type of first-line complementary test should be performed in the relatives of a patient with genetically characterized AHP?

1. It is recommended to offer a genetic study to family members (both symptomatic and asymptomatic) of a patient with AHP of the identified causal genetic variant, and in case of a positive result, perform a baseline biochemical study.

Consensus: 9/9 in agreement

Comments: In the study of family segregation with a known pathogenic genetic variant, direct study using Sanger sequencing is currently cost-effective.[22] In carriers identified through family genetic study, a baseline quantitative biochemical determination of porphyrin precursors (ALA and PBG) in urine is recommended, since there are latent excretory carriers. It is also indicated to perform genetic counseling before and after performing the genetic test.

Although the patient may never develop the disease, given the importance of environmental triggering factors in the development of seizures, recommendations should be provided regarding drugs and other situations that may precipitate them.[22,24] Being aware of being a carrier of AHP reduces the frequency of seizures.[25]

Domain 3: Follow-up of Patients with AHP

PICO 7. Should monitoring that includes determination of porphyrin precursors in the urine of patients with AHP be performed?

1. It is recommended to perform an annual follow-up with determination of porphyrin precursors in urine of all patients who have suffered at least one attack throughout their life and of patients with increased urinary excretion of precursors.
2. It is suggested that patients with latent or inactive porphyria undergo biannual follow-up with determination of porphyrin precursors in urine.

Consensus: 9/9 in agreement

Comments: ALA and PBG levels are related to disease activity and the development of long-term complications.[26] Therefore, it is necessary to monitor patients with AHP, which must be adapted based on the clinical symptoms and biochemical expression.[7] Although the manner and time of how to do this have not been specified, the following monitoring strategy is proposed:

- After an admission for a porphyric attack, it would be appropriate for the review in the clinic to be in the month following discharge to reevaluate the precipitating factors, preventive measures and adequate control of symptoms.
- Patients who have had at least 1 acute attack in their life or those who present increased excretion of porphyrin precursors in urine are more likely to suffer a attack or long-term complications.[4] For this reason, they benefit from adequate monitoring in a reference unit with annual determination of precursors.[4,7] This monitoring may be more frequent depending on the clinical needs of each patient.[27]
- Patients who have never had a attack (latent or inactive porphyria) do not need close clinical follow-up. Despite this, they should also be provided with health education, informing them of the warning signs and precipitating factors of AHP.[27]

PICO 8. Is a positive Hoesch test always diagnostic of an acute attack in a patient with AHP who consults for abdominal pain?

1. In patients with AHP who come to the emergency room due to an episode of abdominal pain, a complete evaluation is recommended to rule out alternative diagnoses.
2. For an optimal assessment of the result of the Hoesch test, the quantitative determination of porphyrin precursors in urine and its comparison with the baseline carried out during follow-up is recommended.

Consensus: 9/9 in agreement

Comments: In patients with a previous diagnosis of AHP who consult the emergency department due to abdominal pain, it is essential to be attentive to the presence of symptoms that support the diagnosis, but also to rule out alternative diagnoses.[4,28] In these patients, normal ALA and PBG levels rule out AHP as the etiology of the symptoms.[29]

In the event that we are dealing with a patient with a history of symptomatic or asymptomatic AHP but not excretory, the positivity of a Hoesch test may be the first screening test suggestive of a new acute attack.[4–6] However, this test is not useful in chronic excretors since the Hoesch test in them is persistently positive.[7] If it is unknown whether a patient with AHP is a high excretor or not, it must be remembered that it is rare for CPH or PV patients to maintain a high excretion of precursors, so in these patients the positivity in the Hoesch test may be suggestive. of a porphyric attack.[30]

On the other hand, although the significant increase in precursors over their baseline level supports the diagnosis of acute attack, this determination is usually not available in the acute moment.[7] Therefore, in a patient with AHP who presents a picture suggestive of an acute attack with a positive Hoesch test and in the absence of an alternative diagnosis, the diagnosis of a porphyric attack should be assumed, and treatment should be initiated, without waiting for the result of the quantification of precursors in urine.

Domain 4: Screening for Long-term Complications in Patients with AHP

PICO 9. Should patients with PHA be screened for hepatocellular carcinoma (HCC)?

1. It is recommended to perform an abdominal ultrasound every 6 or 12 months to screen for HCC in patients over 50 years of age with symptomatic active porphyria.
2. In asymptomatic non-excretory patients or with latent porphyria, it is suggested to dispense with said ultrasound.

Consensus: 9/9 in agreement

Comments: Patients with AHP have a higher risk of HCC, with a prevalence between 1.5–1.8%, being more common in those over 50 years of age.[4,31–33] For all these reasons, it is recommended to perform an ultrasound every 6 or 12 months, which can be individualized according to age, the presence of attacks or the chronic excretion of precursors. Thus, it is recommended to do an abdominal ultrasound every 6 months in patients over 50 years of age. Despite the lack of evidence, less close monitoring could be performed (every 12 months) by interspersing alpha-fetoprotein determination every 6 months.[34] In young asymptomatic non-excretory patients or with latent porphyria, ultrasound could be dispensed with for HCC screening, unless the clinical situation changes, always individualizing according to age and risk factors (obesity, steatosis, viral infection, etc.). In the evaluation of this risk, annual determination of liver enzymes could also be considered, since their elevation has been reported in up to 28% of these patients and could identify a population at risk for the development of long-term complications, such as HCC[4,35].

PICO 10: Should periodic monitoring of blood pressure (BP) and kidney function be performed in patients with AHP?

1. It is recommended to monitor BP and kidney function at least once a year in all patients with active porphyria (sporadic or recurrent).
2. It is suggested to monitor BP and kidney function every 1–2 years in patients with high excretion of precursors, whether symptomatic or asymptomatic, especially if accompanied by other cardiovascular risk factors or in those over 50 years of age.

Consensus: 9/9 in agreement

Comments: patients with AHP have a higher risk of developing arterial hypertension or renal failure, with an incidence greater than 40% and 20%, respectively.[33] In the international and prospective EXPLORE study, which evaluated the natural history of 112 patients with AHP, 68% presented deterioration of glomerular filtration rate (<90 mL/min/1.73 m^2).[36]

The development of high blood pressure and kidney failure in AHP is considered multicausal. On the one hand, porphyrin precursors exert direct damage on the renal cells of the proximal tubules. On the other hand, in acute attacks, the precursors also generate vasoconstriction, which together with the activation of the sympathetic system produces an increase in BP. There is also evidence that the genetic variant of peptide transporter-2 (PEPT-2) confers a greater affinity for ALA at the proximal tubule, causing its reabsorption and contributing to chronic kidney damage.[37]

Determination of kidney function (glomerular filtration rate and/or albumin/creatinine ratio) and BP are extremely simple, so they must be monitored regularly. This monitoring will be more or less close depending on the number of attacks, the urinary excretion of precursors or the presence of other cardiovascular risk factors.[33]

This study has some limitations. First, the selection of experts was arbitrary. However, different specialists with extensive experience in the field of porphyria in various settings were included. Second, the limitations of the DELPHI methodology have already been described previously.[9–12] Despite this, the consensus criteria were previously defined and the vast majority of consensus obtained in the PICO questions supports the solidity of the recommendations. Finally, scientific evidence in this field is evolving, so current recommendations may be modified based on the results of new randomized clinical trials.

In conclusion, the combination of PICO questions and the DELPHI methodology provides a consensus on relevant and controversial issues regarding the approach to patients with porphyria, which allows for improved diagnosis and follow-up.

Ethical considerations

This study has been approved by the Clinical Research Ethics Committee of the Hospital Universitari de Bellvitge (Barcelona, Spain) with approval number PR280/23.

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Conflict of interests

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