Porphyrias: Pathophysiology and clinical management recommendations for hepatologists

VISUAL ABSTRACT

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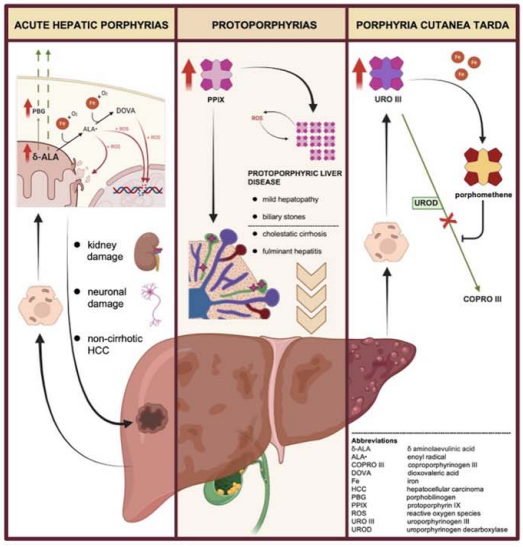

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REVIEW

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Porphyrias: Pathophysiology and clinical management recommendations for hepatologists

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Abstract

In humans, an enzyme dysfunction in heme biosynthesis results in a heterogenous group of diseases collectively known as porphyrias. From a clinical standpoint, porphyrias can be classified as erythropoietic (congenital erythropoietic porphyria—CEP, erythropoietic/X-linked protoporphyria—EPP/XLP) or hepatic (acute hepatic porphyrias—AHPs, porphyria cutanea tarda—PCT), according to the site of organ dysfunction deemed to be responsible for the disease. In terms of total heme production, the liver accounts for the second major heme-synthesizing organ, after the bone marrow. In fact, heme is necessary as a prosthetic group in countless biologic functions, to which hepatic contribution is essential. Furthermore, the pathway of heme biosynthesis is inscribed into a network of fundamental metabolic reactions largely occurring in hepatocytes. Independent of their classification, all porphyrias share some degree of involvement of the liver, either in the pathogenesis, clinical manifestations, or as a preferential target of damage. Crucially, even those types of porphyrias that have been classically defined as erythropoietic do present a hepatic involvement, which can lead to poor clinical outcomes if neglected. Therefore, hepatologists should consider porphyrias as a differential diagnosis for otherwise

Abbreviations: AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; ALA·, enoyl radical; ALA, δ-aminolaevulinic acid; ALAD, δ-aminolaevulinic acid dehydratase; ALAS, δ-aminolevulinate synthase; ALAS1, δ-aminolevulinate synthase (ubiquitous isoform); ALAS2, δ-aminolevulinate synthase (erythroid-specific isoform); APA, acute porphyric attack; APE1, AP endonuclease 1; CEP, congenital erythropoietic porphyria; CPOX, coproporphyrinogen III oxidase; EPP, erythropoietic protoporphyria; F-PCT, familial Porphyria Cutanea Tarda; FECH, ferrochelatase; GATA1, X-linked hematopoietic transcription factor GATA-binding factor 1; HC, hemochromatosis; HCP, hereditary coproporphyria; HFE, human homeostatic iron regulator protein; MRP2, multidrug resistance protein 2; OATP1B1 (*SCLO1B1* gene), solute carrier organic anion transporter family member 1B1; PCT, porphyria cutanea tarda; PEPCK, phosphoenolpyruvatecarboxykinase; PLC, primary liver cancer; PPIX, protoporphyrin IX; ROS, reactive oxygen species; TDO2, tryptophan 2,3-dioxygenase; UROD, uroporphyrinogen III decarboxylase; UROS, uroporphyrinogen III synthase; VP, variegate porphyria; XLP, X-linked protoporphyria.

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unexplained presentations of liver disease. At the same time, a multidisciplinary team dealing with the diagnostic workup and clinical management of all types of porphyrias must include an expert in liver diseases. In this review, we aimed to recapitulate the main aspects of liver involvement in porphyrias, while also providing practical tools to recognize and manage these conditions from the hepatologist's perspective.

Keywords: acute intermittent porphyria, erythropoietic protoporphyria, hepatocellular carcinoma, iron overload, liver damage, porphyria, porphyria cutanea tarda, porphyria variegata

KEY POINTS

- An enzyme alteration in heme biosynthesis results in a heterogenous group of rare diseases collectively known as porphyrias, which are all characterized by a substantial role played by the liver.
- An underlying liver disease should be thoroughly searched for in porphyria cutanea tarda, as this may be the only sign of a hidden liver disease.
- The management of erythropoietic protoporphyrias should focus on preventing systemic complications with a multidisciplinary approach.
- The metabolic alterations occurring in hepatic heme biosynthesis are considered the primary pathogenic mechanism in most acute hepatic porphyrias.
- Regular screening for primary liver cancer should be performed in all patients with a known mutation associated with acute hepatic porphyrias.
- Hepatologists should be aware of porphyrias as a differential diagnosis for an otherwise unexplained hepatopathy.
- It is mandatory to correctly recognize a porphyric patient since the treatment is often very specific but can effectively control the disease.
- In patients with porphyrias, particular attention must be paid to exogenous factors that can favor the development and progression of the disease or trigger exacerbations.
- In order to minimize the risk of a misdiagnosis, local reference centers should be addressed for consultancy whenever a porphyria is suspected.

INTRODUCTION

Heme is a macrocyclic tetrapyrrole, carefully engineered by evolution to exploit the versatile oxidoreductive, gas-binding, and catalytic properties of iron, while minimizing its toxic effects on cells and tissues.[1,2] Even though the majority of heme in mammals is produced by the bone marrow for the purpose of carrying oxygen in red blood cells, the liver accounts for the second major heme-synthesizing organ.[2,3] In fact, the pathway of heme biosynthesis is inscribed into a network of fundamental metabolic reactions largely occurring in hepatocytes.[1] Furthermore, heme is necessary as a prosthetic group in countless reactions and biologic functions.[1] Heme-proteins play an irreplaceable role in nitric oxide biosynthesis (nitric oxide synthases), signal transduction (soluble guanylate cyclases), tryptophan/serotonine metabolism (tryptophan 2,3-dioxygenase, indoleamine 2,3-dioxygenase), homocysteine catabolism (cystathionine β-synthase), general antioxidation and detoxification (catalases, peroxidases, cytochromes of the P450 family), and energy production via oxidative phosphorylation (cytochrome c), among several other key reactions chiefly occurring in the liver.[4]

Heme biosynthesis starts in mitochondria, where glycine and succinyl-coenzyme A are condensed into δ-aminolaevulinic acid (ALA) by ALA synthase (ALAS), the first and rate-limiting enzyme in heme biosynthesis. Two ALA moieties, in turn, are asymmetrically condensed into porphobilinogen, which is then polymerized to hydroxymethylbilane, a linear tetrapyrrole. The latter undergoes cyclization to yield uroporphyrinogen III, which in turn is modified in its side chains to coproporphyrinogen III, then to protoporphyrinogen, and finally protoporphyrin IX. In the last enzymatic step, a ferrous iron atom is chelated into protoporphyrin IX, to yield heme.[1]

In humans, an alteration in the pathway leading to heme biosynthesis results in a heterogenous group of rare diseases collectively known as porphyrias.[5–7] The 8 principal types of porphyrias are each caused by a dysfunction in 1 of the 8 enzymes involved in the heme biosynthetic pathway (Figure 1). The biochemical profile of heme precursor alterations is pivotal for diagnosis.[8] From a clinical perspective, porphyrias can be classified as erythropoietic (congenital erythropoietic porphyria—CEP, erythropoietic/X-linked protoporphyria—EPP/XLP) or hepatic (acute hepatic porphyrias—AHPs, porphyria cutanea tarda—PCT), according to the organ site deemed mainly responsible for the disease.[7] In most

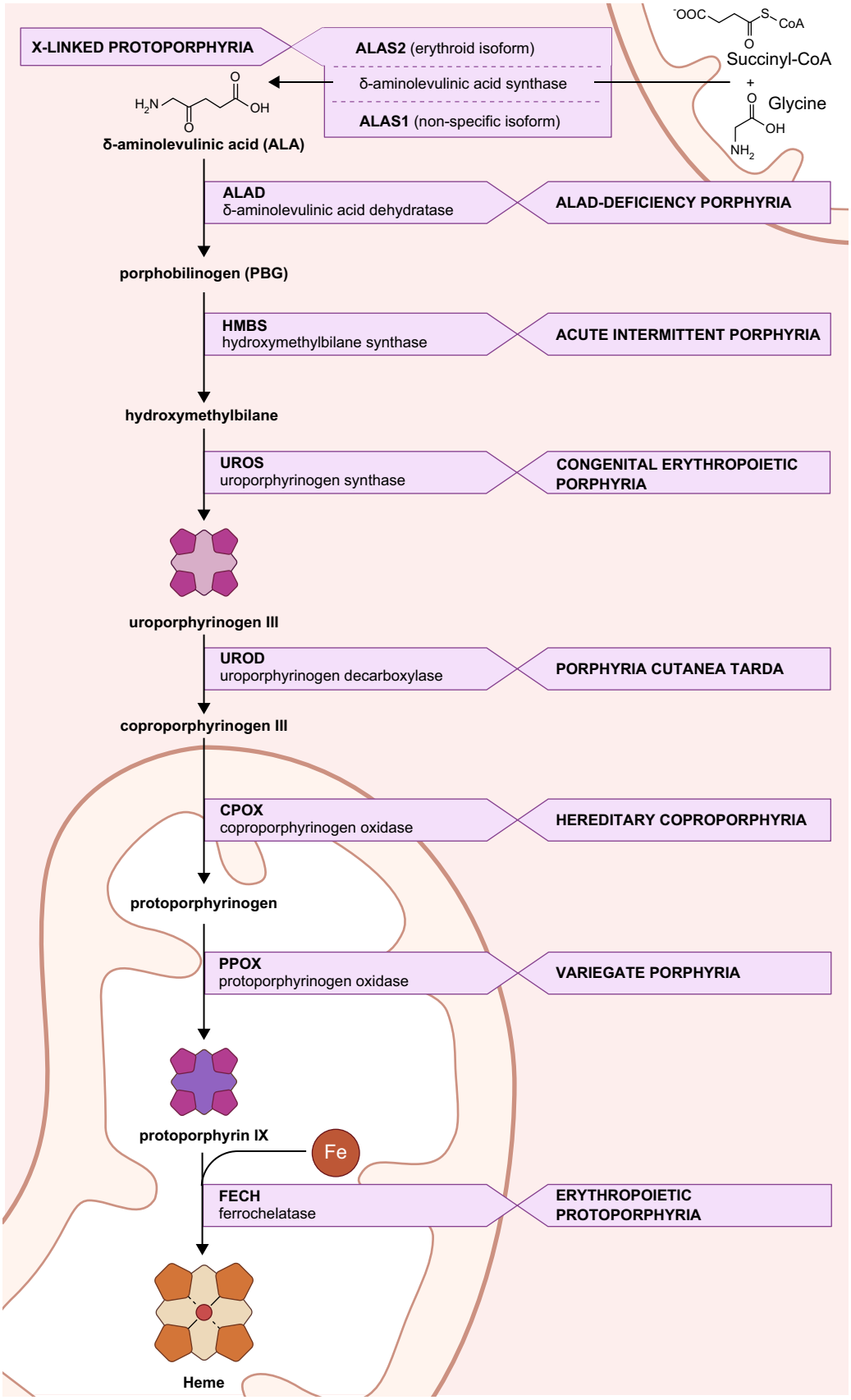

FIGURE 1 Heme biosynthesis and porphyrias.

cases, porphyrias manifest as inherited diseases, except for the sporadic form of porphyria cutanea tarda and some rare cases in which a clonal myelodysplastic population starts producing toxic heme precursors, with clinical pictures resembling some erythropoietic porphyrias (eg, CEP or protoporphyrias).[9,10] Additionally, lead intoxication presents with porphyric manifestations, since lead atoms impair ALA dehydratase by steric hindrance (a similar pathogenic mechanism is engendered by succinylacetone in hereditary tyrosinemia).[11,12]

Independent of their classification, all porphyrias are characterized by a substantial role played by the liver, either in the pathogenesis, clinical manifestations, or as a preferential target of damage (Table 1).

Crucially, even those types of porphyrias that have been classically defined as erythropoietic do present a hepatic involvement, which can lead to poor clinical outcomes if neglected. Therefore, hepatologists need to be aware of porphyrias as a differential diagnosis for otherwise unexplained presentations of a liver disease, from simple hypertransaminasemia to cirrhosis and primary liver cancers. At the same time, increased excretion of porphyrins may be a revealing sign of nonporphyric hepatic damage.

Moreover, the pathophysiology of porphyrias highlights the impact of environmental exposures (exposome) on liver biology and disease.[13] In fact, viral, chemical, and hormonal agents can influence the development, progression, and expressivity of most disease forms.

This review aims at recapitulating the main aspects of liver involvement in porphyrias while also providing practical tools to recognize and manage these conditions from the hepatologist's perspective.

PORPHYRIA CUTANEA TARDA

Clinical features and etiology

Patients affected by porphyria cutanea tarda (PCT) suffer from painful, blistering bullae or erosions arising after exposure to sunlight. Such lesions are usually roundish and subcentimetric, heal slowly and leave scars, and occur most typically in the back of hands or fingers, or around the mouth. Additionally, sun-exposed areas may be affected by altered skin pigmentation or hair growth (hypertrichosis).[14,15]

Approximately 80% of patients with PCT are affected by the acquired, sporadic type PCT, whereas the presence of a germline heterozygous mutation of uroporphyrinogen III decarboxylase (UROD) causes the inherited form of the disease (familial PCT, F-PCT).[15–17] Hepatoerythropoietic porphyria, in contrast, is the term for the condition caused by homozygous pathogenic *UROD* variants, which presents similarly to PCT, even if clinically more severe.[15,18,19]

Mechanisms of disease

In patients with PCT, hepatic UROD activity is usually reduced to ~25%.[20–22] However, even in the presence of a genetic enzyme dysfunction, the protein production rate is usually half the normal at least. This finding has led to a hypothesis of the presence of a competitive UROD inhibitor, which has been eventually characterized as a uroporphomethene moiety.[22] Uroporphomethene is produced by the iron-dependent, partial oxidation of one bridge carbon in the tetrapyrrolic macrocycle of uroporphyrinogen.[22] Cytochrome 1A2 of the P450 family likely plays a catalytic role in the reaction, as it is essential for causing uroporphyria in rodents.[14,22,23]

Role of cofactors

Patients with both sporadic type PCT and F-PCT do not usually develop the disease unless in the presence of other causes of liver disease,[17,24–26] which almost universally involve a condition of liver iron overload.[17,26–30] Of note, iron supplementation therapy usually worsens PCT symptoms, whereas dietary regimens reducing total iron content have been reported as beneficial.[31] Hemochromatosis (HC), HCV infection, and alcohol-associated liver disease are among the most common forms of chronic liver disease associated with overt PCT.

Hemochromatosis The association of PCT with the presence of pathogenic variants in the human homeostatic iron regulator protein (HFE), which is responsible for the most common form of HC, has been extensively investigated.[29,32–37] In particular, the p.C282Y\p.C282Y genotype is markedly more represented in patients with PCT compared to the general population, together with the compound heterozygous p.C282Y\p.H63D genotype, which in the presence of other acquired factors can predispose to a milder form of iron overload.[29] Interestingly, it has been reported that patients with PCT have significantly reduced expression of hepcidin, independent of *HFE* genotype.[38] Hepcidin is considered the master regulator of iron metabolism in humans, and its deficiency—either acquired or caused by inherited diseases, as in HC—usually leads to iron overload phenotypes.[39]

HCV infection A strong association between PCT and HCV infection has long been identified, especially in Southern Europe. In fact, HCV infection seems to induce an inadequate hepcidin response to iron accumulation.[40] Furthermore, liver specimens of patients with PCT with HCV-related hepatopathy showed a higher iron accumulation compared to HCV-infected patients without PCT.[40] Although the exact mechanism that links chronic HCV infection to the pathogenesis of PCT remains unknown, it is interesting

TABLE 1 Liver involvement in porphyrias

Disease	Liver manifestations	Liver involvement in pathogenesis	Notes on disease management
Porphyria cutanea tarda	Possibly more severe histologic signs of hepatopathy	Liver iron accumulation causes the disease in predisposed individuals	• Symptoms regress with liver iron depletion or resolution of liver inflammation • Mandatorily search for an underlying, sometimes hidden cause of hepatopathy (eg, HCV, alcohol abuse, hemochromatosis) and treat it if possible • Symptoms are managed effectively through phlebotomy or chloroquine/ hydroxychloroquine therapy (beware of liver toxicity)
Erythropoietic/ X-linked protoporphyrias	• Chronic liver disease from mild hypertransaminasemia to cirrhosis • Intrahepatic cholestasis • Protoporphyric gallstones • Acute (fulminant) cholestatic hepatitis	In EPP, a small amount of protoporphyrin accumulation in the liver could be due to endogenous (hepatocellular) *FECH* deficiency	• Screen for HCC (mainly because of underlying chronic liver disease) • Protoporphyric hepatopathy should be specifically managed with a multidisciplinary follow-up and treatment • Several off-label therapies have been attempted for chronic liver manifestations, UDCA is probably the most effective to date • Avoid or treat other causes of liver disease (alcohol, viral, drugs, metabolic dysfunction associated) • Beware of cholestatic complications, from the standard management of biliary stones to prevention of cholestatic acute hepatitis • If a protoporphyric acute hepatitis is suspected, promptly refer to a local reference center for diagnosis and treatment • Liver transplantation is not curative, but must be considered in advanced/fulminant hepatopathy • Use light filters to avoid complications (eg, light-induced peritoneal damage) during surgery • As skin phototoxicity can be mild, EPP/XLP should be ruled out in cases of unexplained elevations of liver enzymes, when more common causes have been excluded
Congenital erythropoietic porphyria	Intrasinusoidal extramedullary erythropoiesis may lead to liver fibrosis		• Iron chelation may revert spleen and hepatic signs of damage • Phlebotomy is effective in suitable patients
Acute hepatic porphyrias • Acute intermittent porphyria • Variegate porphyria • Hereditary coproporphyria • ALA dehydratase deficiency	• Hypertransaminasemia • Noncirrhotic primary liver cancer • Alterations in amino acid (tryptophan, homocysteine) metabolism and bioenergetic profile • Hemin-induced liver iron overload	Overproduction of heme precursors by the liver is considered the primary mechanism of damage (ALAD deficiency is a likely exception, as it does not seem to respond to liver-targeted therapies)	• AHPs should be ruled out in cases of unexplained elevations of liver enzymes, when more common causes have been excluded • If an APA is suspected, stop/avoid potential triggering factors and promptly refer to a local reference center for diagnosis and treatment • Heme arginate, glucose infusion, support therapy, and trigger avoidance are the mainstay in the management of APAs (beware of liver iron overload with chronic hemin therapy) • Liver transplantation is curative • Givosiran is specifically targeted to inhibiting ALAS1 translation in hepatocytes (beware of kidney and liver-related adverse events, which can be severe—rarely)

Abbreviations: AHP, acute hepatic porphyrias; APA, acute porphyric attacks; EPP/XLP, erythropoietic/X-linked protoporphyria; UDCA, ursodeoxycholic acid.

to note that HCV-infected patients frequently present an increased coproporphyrinuria, with an altered coproporphyrin (CP) I/III ratio as well as a correlation, albeit weak, between total porphyrin excretion and laboratory markers of impaired liver function.[41,42] Recent findings suggest that the HCV core protein may play a role in these alterations.[43] While this findings may help to shed light on the pathogenesis of HCV-related PCT, it is important to note that patients with HCV and increased coproporphyrinuria do not usually present with clinical signs of PCT.[43]

Ethanol Alcohol-associated liver disease is a well-characterized condition that predisposes to hepatic iron overload, since ethanol inhibits hepcidin expression and leads to an increase in intestinal iron absorption.[44,45] Furthermore, chronic alcohol liver disease is characterized by a decreased activity of hepatic UROD.[46] Instead, acute alcohol ingestion inhibits liver coproporphyrinogen III oxidase (CPOX), which is then counter-regulated by an increase in ALA synthase activity and heme turnover (in fact, secondary coproporphyrinuria is also frequent in alcohol consumption).

Other cofactors Other susceptibility factors for PCT have been identified in estrogen use and smoking; while the latter is a well-known inducer of Cytochrome 1A2 of the P450 family (as is ethanol), it is still unclear why estrogens may pose a risk for developing PCT. Importantly, associations between different risk factors (eg, HCV infection with alcoholism) are usually observed in patients with PCT, thus emphasizing the role of behavior-related factors in the development of the disease in susceptible individuals.[17] It is worth noting that HIV infection has been frequently detected in patients with PCT (13%),[17] likely because of coinfection with HCV.[47] Interestingly, HIV can be detected in the blister fluid of seropositive patients with PCT.[48] Finally, some case reports have started to raise awareness about a possible role of metabolic-associated fatty liver disease as a predisposing factor for PCT.[49,50] In this regard, it remains to be determined whether metabolic hyperferritinemia may play a precipitating role.[51]

Histological features

Even though the most dramatic manifestations of PCT are cutaneous, a few early histology studies observed disease-specific hepatic lobular lesions in different populations of patients with PCT. These lesions were especially present in patients who used alcohol and estrogen therapy, corroborating the role of these factors in the exacerbation of the disease. The liver tissue of PCT-affected patients displayed iron-rich KCs, fat accumulation, inflammatory mononuclear cells, and collagen deposition[52]; most of these are aspecific findings that can also be found in viral hepatitis, HC, or in patients under hemodialysis. Another study highlighted that needle-like (acicular) inclusions in the cytoplasm of hepatocytes appeared to be a specific marker of PCT, as they were not found in other types of porphyrias nor in other known diseases or organs; another specific marker was positive autofluorescence in fresh cryostatic sections left to air-dry.[53]

Clinical pearls for the hepatologist

Therapeutic approach

Look for the culprit After a PCT diagnosis is formulated, it is mandatory to look for a triggering hepatopathy. The mainstay of PCT management consists of the treatment of the underlying cause of liver disease, as treating the latter often results in complete resolution of cutaneous manifestations and reduction/normalization of urinary uroporphyrin levels. For example, HCV eradication in infected patients with active PCT usually leads to resolution of PCT with normalization of urinary porphyrin levels.[40] In this regard, it is worth mentioning that direct-acting antiviral medications are effective and safer than previous therapies, as interferon-based regimens would sometimes worsen PCT symptoms in the initial phases of treatment.

Iron depletion and other therapies It should be underlined that a cause of hepatopathy should always be searched thoroughly, as sometimes PCT with liver iron overload is the only sign of hidden, rare liver diseases (eg, isolated liver sarcoidosis in the authors' experience and others). However, a remission of symptoms can also be obtained through iron depletion therapy, which can be implemented through phlebotomy unless contraindicated (eg, patients with cirrhosis with severe anemia, or patients with iron-loading myelodysplastic syndromes).[30,54,55] In some cases, therapy with the iron chelators desferrioxamine or deferasirox has been successfully attempted,[56,57] whereas to the best of our knowledge deferiprone has only been used in animal studies.[58]

Oral hydroxychloroquine (or chloroquine) can be preferred to phlebotomy when serum ferritin levels are not exceedingly high (ie, <500 ng/mL).[15,59] The mechanism of action of 4-aminoquinoline compounds likely involves lysosomal disruption eg, increasing lysosomal pH, which facilitates the release of accumulated porphyrins from hepatocytes for clearance by the kidneys.[60,61] Otherwise, 4-aminoquinoline compounds could decrease intracellular iron content[59,62] or even reduce ALAS activity.[14,60,63,64] Crucially, 4-aminoquinoline compounds can cause liver damage by

themselves; it is therefore important to use low-dosage regimens to avoid drug-induced acute hepatitis (hydroxychloroquine 100 mg or 200 mg twice weekly, or chloroquine 125 or 250 mg twice weekly) and to pay attention to factors possibly affecting safety (exclude pregnancy, avoid concomitant use of other hepatotoxic drugs, regularly perform ophthalmologic examination, and monitoring of liver biochemistry). In this regard, quantification of liver iron content through magnetic resonance T2*-weighted imaging can provide a more complete characterization of the iron status of a patient, and support phlebotomy over 4-aminoquinolines even in patients with borderline serum ferritin values but evidence of clinically significant liver iron overload. Phlebotomy and 4-aminoquinoline compounds therapy may also be combined in patients resistant to single treatment. Finally, erythropoietin can be used effectively in this setting, as it mobilize liver iron stores.[48,65]

Liver cancer in PCT The occurrence of HCC in patients with PCT has been variously reported and investigated. Several authors have suggested that the presence of PCT poses patients at high risk to develop HCC,[53,66–69] in particular, when patients with cirrhosis with and without PCT are compared[66]; moreover, it has been highlighted that HCC may occur in patients with PCT with a long symptomatic period before the start of the treatment.[68] At least one study reported a correlation between age and liver damage; hepatic architecture distortion was detected at a mean age of 48 years, while cirrhosis and HCC occurred at a mean age of 57 and 67 years, respectively.[53] Notably, PCT was identified as an independent risk factor for the development of HCC in at least 1 prospective study.[70] In contrast, some case series have not found an increased risk of HCC in patients with PCT.[71–74] Be that as it may, it is doubtlessly advisable to have patients with PCT monitored with a regular follow-up, according to the severity of the underlying liver condition, which likely precipitated PCT; liver biochemistry and abdominal imaging every 6–12 months should be considered for patients with advanced fibrosis, and a low threshold for alertness should be maintained to detect early signs of advanced liver disease or cirrhosis.

ERYTHROPOIETIC PROTOPORPHYRIAS

Clinical features and etiology

EPP is usually inherited in a pseudodominant autosomal pattern, caused by a compound heterozygosis in the ferrochelatase (*FECH*) gene. Patients with EPP carry an inactive *FECH* allele as well as an intronic, in trans-hypomorphic haplotype, which is quite common in the general population (c.315-48T > C, previously known as IVS3-48T/C).[75,76] Ferrochelatase activity in patients with EPP is ~10%–30% of normal.[75] Gain-of-function variants in the erythroid-specific ALAS isoform (ALAS2) cause X-linked protoporphyria, which presents with clinical manifestations similar to EPP, although it is rarer and has been differentiated from the latter only in 2008. Finally, another rare form of protoporphyria has been described in association with pathogenic variants in the mitochondrial unfoldase *CLPX*.[77]

Independent of the causing mutation, protoporphyrins accumulate in multiple sites, most notably the bone marrow, plasma, erythrocytes, and the liver. Crucially, protoporphyrin IX (PPIX) deposits in plasma undergo type I/II photosensitized reaction and cause light-dependent toxicity. Therefore, the cutaneous involvement is usually the most burdensome for patients with EPP.[78,79] Proportional to the duration and intensity of sunlight exposure—as well as to humidity and the timing of previous exposures—skin manifestations range from a mild cutaneous discomfort to painful, burning reactions that compel patients to avoid any exposure to sunlight. The erythropoietic manifestations of protoporphyrias, instead, consist mainly of mild microcytic hypochromic anemia and thrombocytopenia, possibly due to ineffective erythropoiesis.[80–85]

Liver involvement Protoporphyric hepatopathy can be observed in a significant minority of patients with EPP/XLP[86,87] and may present as (1) cholelitiasis (especially in younger patients) with formation of protoporphyrin biliary gallstones, (2) chronic parenchymal disease, manifesting as an elevation in the markers of hepatocytolysis and cholestasis, (3) progressive hepatocellular disease, (4) fulminant cholestatic hepatitis (1%–5% of patients with hepatopathy), featuring an acute and rapidly progressive liver failure, which may require liver transplantation.[87,88] Although liver steatosis and elevated liver stiffness may not be overrepresented in patients with EPP/XLP, compared to the general population,[89] it should be remarked that protoporphyrin toxicity is an independent, additional cause of liver damage, with higher levels of protoporphyrins likely correlating with more severe hepatic involvement.

It is worth noting that some patients are only mildly symptomatic for skin phototoxicity, but may nevertheless suffer from liver damage. Therefore, protoporphyria should be considered in cases of unexplained hypertransaminasemia, after other more common causes have been ruled out, since mild hepatopathy with negligible skin photosensitivity could be the only or most noticeable sign of protoporphyria.

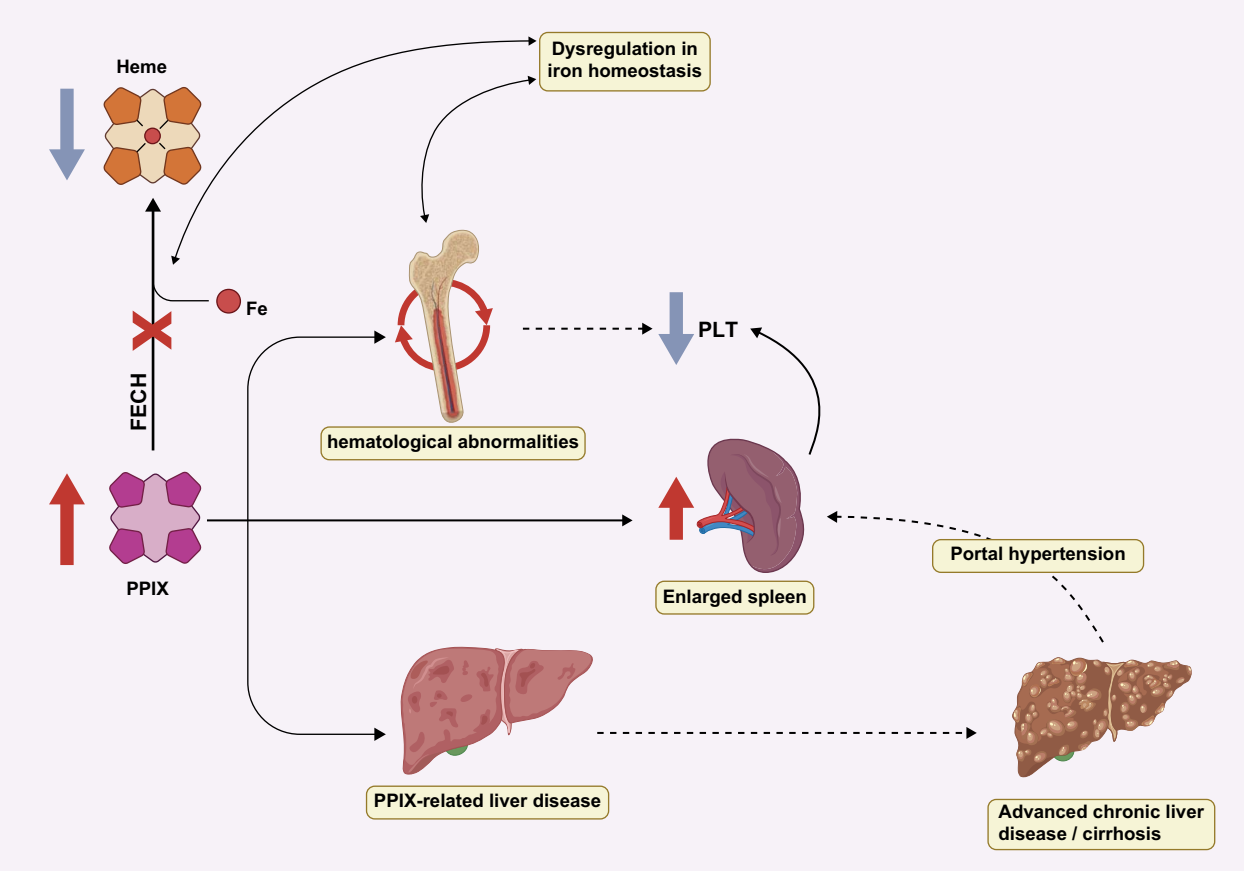

FIGURE 2 Erythropoiesis and liver status in protoporphyria: a model for a complex interplay. A significant minority of patients with protoporphyria present with mildly increased spleen dimensions and thrombocytopenia without overt signs of portal hypertension.[85] Although further investigations are warranted, a pathophysiological model can be proposed in which an increased erythropoietic drive is primarily responsible for the observed alterations before advanced liver disease develops. Created in https://BioRender.com. Abbreviations: FECH, ferrochelatase; PLT, platelets.

Mechanisms of disease

Since hydrophobic protoporphyrins accumulate in hepatocytes as well as the biliary system, patients with EPP/XLP are at risk of so-called protoporphyric hepatopathy.[83,90]

In physiological conditions, protoporphyrins are excreted via the bile canaliculi and are minimally reabsorbed in the gut through enterohepatic circulation.[91] In protoporphyrias, the progressive accumulation of protoporphyrins leads to the formation of insoluble crystals, with cholestatic effects and morphologic alterations in the hepatobiliary system, and a potential progression from mild inflammation to fibrosis and cirrhosis,[87,92] further impairing the disposal of protoporphyrin deposits.

Several studies have contributed to clarifying the mechanisms of light-independent porphyrin toxicity:[93] cell-damaging effects may be related to noncovalent, oxygen-dependent, reversible protein aggregation triggered by cytoplasmic, extralysosomal porphyrin accumulation.[94,95] Hepatocytes are particularly susceptible to injury to intermediate filaments (cytoplasmatic keratins and nuclear lamins),[93,96] endoplasmic reticulum (eg, calnexin and protein disulfide isomerase),[97] proteasome regulatory particles, and glycolytic enzymes such as glyceraldehyde 3-phosphate dehydrogenase.[97] Oxidizing processes such as inflammation or redox reactions could both trigger and be induced by porphyrin accumulation,[94] allowing porphyrins to unleash reactive oxygen species (ROS) production as well as intracellular protein aggregation without the need for prior photosensitization. In this regard, it is worth noting that P450c cytochromes and NADPH reduce uroporphyrin I, yielding superoxide radical (O_2^-).[98,99]

Role of modifiers Even though the precise mechanisms responsible for liver damage have yet to be thoroughly clarified, the possible contribution of genetic disease modifiers has been hypothesized.[100] For instance, it has been suggested that a role could be played by the ATP-binding cassette superfamily G member 2 transporter, which mediates protoporphyrin distribution, metabolism, and excretion into the biliary system,[101] and whose deficiency could protect against protoporphyric hepatopathy.[101] A common variant of this transporter (T521S), which impaired protein

expression in vitro, was detected in a patient with EPP who underwent fatal liver failure.[102] In vivo, a dysfunction in the porphyrin transporter ABCB6 exacerbated liver injury in Fech-deficient mouse model, with accumulation of protoporphyrin crystals in hepatocytes, parenchymal architectural disturbances, and an increase in total serum bilirubin and markers of liver damage and inflammation.[102] However, a following study on allelic frequency of *ABCB6* variants in patients with porphyria did not detect significant phenotype associations in EPP, either between severely and mildly symptomatic patients, or compared with the general population.[103]

Histological features

Protoporphyrin crystals have been associated with ultrastructural damage in hepatocellular nuclei, endoplasmic reticulum, plasma membranes, and bile canaliculi, even in the early phases of EPP/XLP.[104] In vivo, it has been observed that exposure to high PPIX levels causes periportal or septal fibrosis, as well as an atypical ductular reaction.[105] Since protoporphyrins bind to bile components and disrupt the balance between phospholipids, bile acids, and cholesterol, it has been suggested that retention of PPIX in hepatocytes and KCs could be protective through decreasing the amount of lipid-free bile acid and preventing the development or progression of cholestatic complications.[106] At the histological level, intracellular protoporphyrins precipitate with a very specific "Maltese cross" appearance, detected through fluorescent birefringence.[87,107–109] Some accumulation of α 1-antitrypsin in KCs has also been observed.[110]

Clinical pearls for the hepatologist

Principles of management From a clinical perspective, the management of EPP/XLP should be focused not only on dermatological evaluations, but also on preventing systemic complications.[111,112] As no large, controlled trials have been conducted to establish the validity of some specific approach to protoporphyric hepatopathy, the management of this rare disease mainly relies on expert consensus guidance. In this regard, Levy et al,[113] on behalf of the Porphyrias Consortium of the Rare Diseases Clinical Network, recently published evidence-based consensus guidelines which summarize the most up-to-date indications for the management of protoporphyria-related liver dysfunction.

Monitoring of liver function with blood chemistry (complete blood count, international normalized ratio, serum liver enzymes), with a particular attention to abnormalities in the laboratory markers of cholestasis (bilirubin total and conjugated, γ-glutamyl transferase, and ALP), as well as an imaging assessment (eg, abdominal ultrasound) should be performed periodically, ie, every 6–12 months depending on the clinical history of the patient. A recently proposed algorithm recommended that liver function be regularly tested along with erythrocytes PPIX content and coproporphyrin urinary excretion (with I/III isomer ratio),[114] also based on a long-term study on the clinical history of patients with protoporphyria, which highlighted an increase in coproporphyrinuria with alterations in the I/III isomer ratio as a possible "red flag" for impaired protoporphyrin biliary excretion and an early sign of hepatic decompensation).[86]

Understanding the severity of liver involvement It is not uncommon for patients with protopophyria to present with decreased platelet counts, alterations in liver enzymes, and mildly increased spleen dimensions.[85] To the eyes of a hepatologist, these alterations could prompt a suspicion of portal hypertension, which must be ruled out. However, our group and other groups reported that increased spleen dimensions, other than decreased platelet counts, are likely a basal manifestation of protoporphyria, which can be found independent of the liver status of patients with protoporphyria.[85,115] In this regard, Figure 2 proposes a model that aims to recapitulate some aspects of the complex interplay between erythropoiesis and liver status in protoporphyria.

Be that as it may, portal hypertension is a dreaded complication of protoporphyric hepatopathy, and in our experience, the usual noninvasive tests for fibrosis and clinically significant portal hypertension (ie, liver stiffness, biochemistry-based prognosis scores), validated on other types of chronic liver diseases, are not always reliable[116,117] although their usefulness is still under investigation.[118] Furthermore, a case report from our group provided indirect evidence that portal hypertension in EPP appears to be strictly sinusoidal, unlike other cholestatic liver diseases such as primary biliary cholangitis.[117]

Avoidance of risk factors Since severe liver dysfunction can be precipitated by exogenous agents,[119] exposure to hepatotoxic factors should be minimized. Therefore, patients should be encouraged to abstain from alcohol and adopt a lifestyle and dietary regimen aimed at preventing the onset of metabolic dysfunction–associated steatotic liver disease. Patients should be screened for the most common hepatotropic viruses (HAV, HBV, and HCV), and vaccination against HAV and HBV should be proposed. Hepatotoxic drugs should be administered with caution. Other less common causes of liver disease, especially cholestatic (eg, immune-mediated) hepatopathies, should be excluded. In the latest consensus guidelines,[113] caution is warranted on the use of oral contraceptives containing high-dose estrogen (ie, >35 μg ethinyl estradiol), given a potential risk for worsening cholestasis, although contraceptive-related cholestasis has not been associated with protoporphyric hepatopathy yet.

Therapeutic approach

Blood transfusion It has been suggested that erythrocyte transfusion at higher hemoglobin thresholds (eg, 9–10 g/dL) may benefit patients with EPP/XLP, even in the absence of clinical signs of anemia, through suppression of erythropoietin release from kidney interstitial cells.[120] At least in our experience, though, this approach is rarely adopted, as patient usually have very mild anemia (differently from what happens to patients with CEP), and the risks associated with erythrocyte transfusion are not negligible.[121]

Biliary detoxifiers As a protective measure, the formation of biliary sludge and protoporphyrin gallstones should be prevented. Some studies have reported that a combination of chenodeoxycholic acid and ursodeoxycholic acid may enhance biliary elimination of PPIX.[122,123] Although no significant effect was reported in mice,[124] a recent study highlighted several putatively beneficial effects of ursodeoxycholic acid in *Fech−/−* deficient zebrafish.[125] As a matter of fact, therapy with 13–15 mg/kg/d of ursodeoxycholic acid is probably the most diffuse and commonly recommended in the management of mild-to-moderate protoporphyric hepatopathy.[113] Cholestyramine, a bile sequestering agent, might reduce the protoporphyrin plasma levels by interrupting their enterohepatic circulation,[124,126] although its effective clinical role is debated.[127] Likewise, lactulose is expected to inhibit the reabsorption of bile acids, thus decreasing the enterohepatic circulation of protoporphyrins. Furthermore, it has been historically known that a metabolite of cimetidine acts as an effective reversible inhibitor of hepatic ALAS1 activity.[128] Following this evidence, cimetidine has been successfully employed in the treatment of EPP in both adult and pediatric settings.[129–132] Although several case series have reported an amelioration of symptoms and liver biochemistry, sometimes with a significant decrease in PPIX levels, the efficacy of cimetidine treatment has been recently questioned as it has never been formally assessed in randomized controlled trials.[113,133]

Further treatment options In the course of the rapidly progressive phase of liver disease, a reduction in protoporphyrin uptake by liver cells can be attempted with i.v. administration of hemin,[134–136] plasmapheresis,[137] or LDL apheresis (LDL are major carriers of protoporphyrins).[137] It has been reported that also vitamin E, which has liver antioxidant effects, decreases erythrocyte PPIX concentration when administered intravenously.[138]

Liver transplantation Liver transplantation should be considered for patients with EPP/XLP with end-stage chronic liver disease,[88] as well as an emergency treatment for fulminant EPP-associated cholestatic hepatitis. More than 50 transplants for protoporphyric end-stage liver disease have been reported, with survival rates of 47%–66% after a 10-year follow-up.[139] Liver transplantation is effective in restoring liver function, although it does not resolve the enzyme abnormality in erythroid cells and does not lessen liver exposure to plasma protoporphyrins. Therefore, there is a risk of recurrence of EPP/XLP-related hepatopathy even after a liver graft, as a definitive cure can be obtained only through hematopoietic cell transplantation.[140] In a few cases, the 2 procedures have been performed sequentially.[141] In this regard, bone marrow transplantation could potentially restore liver function without needing a liver graft, provided that cholestasis is controlled by medical treatment and there is no advanced liver fibrosis.[142] Possibly because of the persistence of protoporphyrin biliary excretion, EPP/XLP transplanted patients are more susceptible to biliary complications compared with other liver graft recipients. Therefore, it has been recommended that a Roux loop should be preferred over duct-to-duct anastomosis to allow safer bile drainage.[143] As protoporphyrins accumulate in intra-abdominal tissues, special care should be taken in adequately filtering the light from surgery lamps, to avoid perioperative complications (eg, bowel perforation due to protoporphyric light-dependent injury to the peritoneum), which can be catastrophic.[88,144,145]

CONGENITAL ERYTHROPOIETIC PORPHYRIA

Clinical features and etiology

A biallelic impairment of uroporphyrinogen III synthase (UROS)—or, less frequently, X-linked hematopoietic transcription factor GATA-binding factor 1—causes congenital erythropoietic porphyria (CEP), also known as Günther's disease.[146–148] In CEP, hydroxymethylbilane cannot undergo UROS-mediated conversion to uroporphyrinogen III, but is instead rerouted toward nonenzymatic cyclization, thus yielding porphyrin isomer I compounds—uroporphyrinogen I and coproporphyrinogen I. As CPOX is stereospecific for the III isomer, both cyclic I isomers undergo nonenzymatic oxidation, respectively, to uroporphyrin I and coproporphyrin I,[147,149] altering their respective I/III isomer ratios.

Clinical manifestations range from mild photosensitivity to devastating blistering lesions, which ultimately result in deformities by photomutilation in the sunlight-exposed areas. Intravascular hemolysis, which can be very severe, and ineffective erythropoiesis both lead to iron-loading anemia.

Clinical pearls for the hepatologist

Liver involvement is uncommon, although a complete characterization is probably lacking due to the rarity of the disease.[150] The most frequently reported liver manifestations in adult patients with CEP are aspecific (hepatomegaly, alterations in liver enzymes) with severity widely ranging from asymptomatic to cirrhosis; splenomegaly, on the contrary, is often present and can be massive.[150] A case report described liver fibrosis with signs of diffuse intrasinusoidal extramedullary hematopoiesis (featuring several erythroid precursors in the context of sinusoidal congestion and dilation), possibly as a result of iron-loading chronic anemia.[151] Recently, another report described portosinusoidal liver disease, with obliterative portal venopathy, nodular regeneration, bridging fibrosis, and pigmented KCs;[152] in this case, the severity of the hepatic decompensation first required TIPS and eventually liver transplantation. In fact, CEP mouse models[153] display a predominantly Kupfferian iron accumulation pattern, together with iron-loaded and enlarged spleens suggestive of compensatory extramedullary erythropoiesis.[154] In the same model, the oral iron chelator deferiprone was able to decrease the number of erythroid clusters from extramedullary erythropoiesis in the liver and the spleen, as well as reverse the skin symptoms and hematological abnormalities.[155]

Therapeutic approach
Consistent with the erythropoietic nature of the disorder, bone marrow transplantation is potentially curative in CEP.[148,156] In the presence of a suitable donor and according to the phenotype, genotype, and biochemical profile of the disease, hematopoietic stem cell transplantation should always be considered in the management of CEP,[148,156,157] although a recent case series reported unexpectedly high rates of liver disease in recipients of CEP.[157] Otherwise, inducing iron deficiency in patients with CEP alleviates the disease phenotype,[2] as it inhibits iron-induced ALAS2 activity, suppressing the erythropoietic pathway and decreasing the buildup of heme precursors. Given the suboptimal safety profile of iron chelation, patients can benefit from repeated phlebotomies, with smaller blood volumes removed compared to regular phlebotomies to account for CEP-related anemia.[158,159]

ACUTE HEPATIC PORPHYRIAS

Clinical features and etiology

Acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and the ultra-rare ALA dehydratase deficiency porphyria (Doss disease) are collectively known as acute hepatic porphyrias (AHPs). All AHPs are autosomal dominant with an estimated low penetrance, except Doss disease, which is autosomal recessive. A hallmark feature of AHPs is the occurrence of acute porphyric attacks (APAs), which comprise a wide spectrum of potentially life-threatening neurovisceral manifestations—including polyneuropathy, cardiac, and gastrointestinal dysautonomias (eg, arrhythmias, paralytic ileus, and paralysis), as well as central manifestations such as hyponatremia from inappropriate antidiuretic hormone secretion, seizures, psychiatric disturbances, and clinical pictures reminiscent of posterior reversible encephalopathy syndrome. Furthermore, several patients affected by AHPs suffer from long-term complications or chronic manifestations of the disease, such as porphyria-associated kidney disease, noncirrhotic primary liver cancer (PLC), chronic neuropathy, or chronic pain syndrome.[4,160–163]

In AHPs, the metabolic alterations that occur in hepatic heme biosynthesis are considered the primary cause of the disease. A likely exception is represented by ALAD deficiency, as poor results have been reported with liver-targeted therapies in these patients[164–166]; in this case, a significant pathogenic role could be played by bone marrow abnormalities.[165,166]

Mechanisms of disease

In the presence of exogenous or endogenous stimuli that trigger an increase in the body's demand for heme (ie, hormonal fluctuations, alcohol intake, fasting, particular “porphyrinogenic” drugs[167,168]), ALA synthase 1 (ALAS1) is upregulated.[169,170] Patients with AHPs are unable to fully channel the increased production of heme precursors through every enzyme step in the pathway,[170] yielding a buildup of toxic heme precursors. Most neurovisceral manifestations of APAs are deemed to be caused by increased levels of ALA,[170–172] which is produced in excess in all forms of AHPs. Consistent with the specific enzyme deficiency that causes the disease, an increase in porphobilinogen (in AIP, VP, and HCP) or also in cyclic porphyrin levels (in VP and HCP) can be observed; in the latter case, cutaneous deposition of photoreactive cyclic porphyrins can cause photosensitivity and skin manifestations that resemble PCT.

Alterations in tryptophan metabolism Several lines of evidence suggest that patients with AHP may suffer from dysregulations in the metabolism of amino

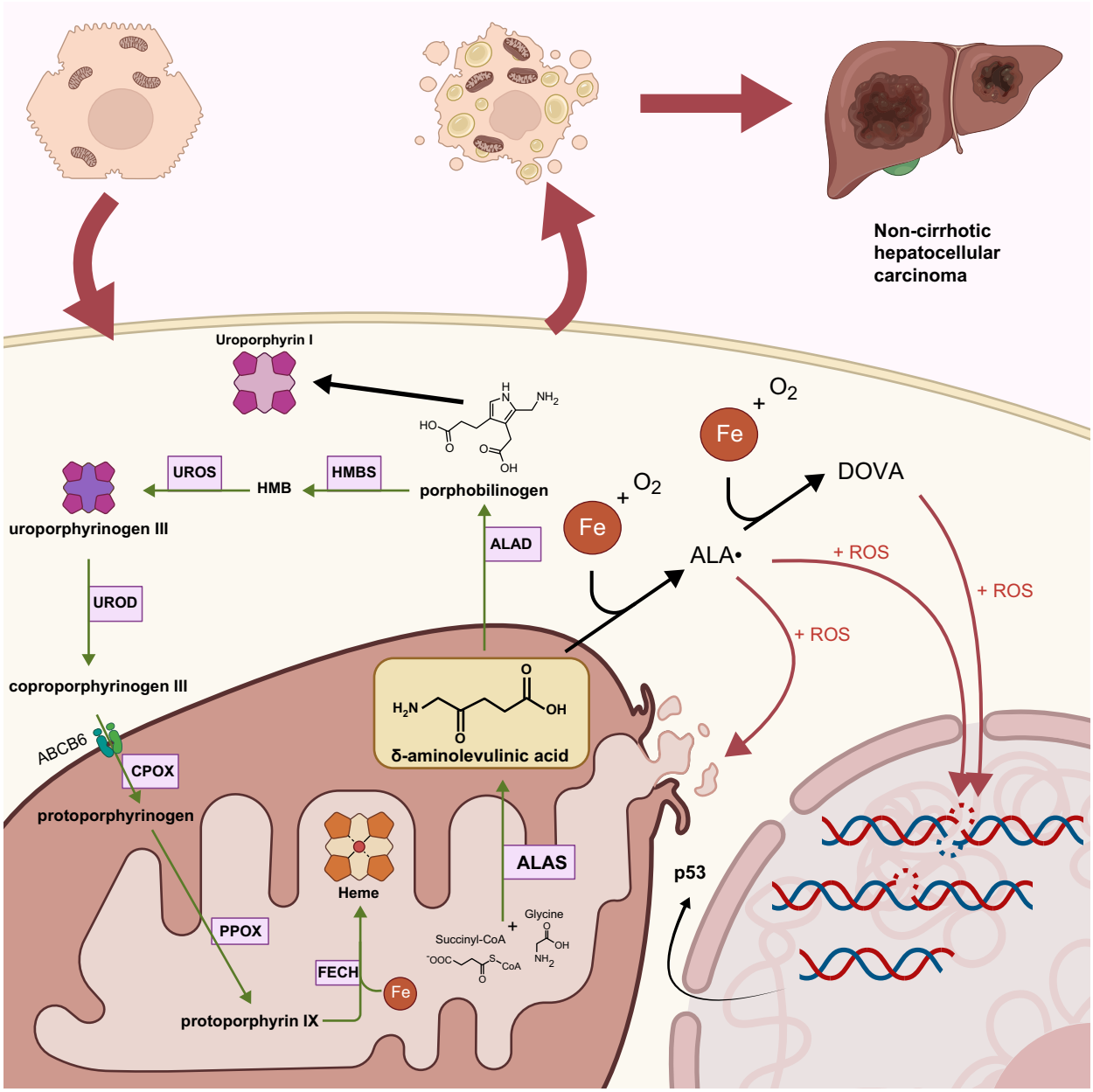

FIGURE 3 Mechanisms of liver damage in acute hepatic porphyrias. In the presence of iron and oxygen, ALA undergoes a phosphate-catalyzed autoenolization to yield the oxidizing species superoxide anion, HO· radical, and enoyl radical (ALA·). In a following step, ALA· is oxidized by iron to DOVA, a DNA alkylating agent. Additionally, ALA-driven oxidative damage alters the permeability of the mitochondrial membrane. Porphobilinogen buildup could theoretically result in excess noncatalyzed cyclization to uroporphyrin I and subsequent more hydrophobic moieties, which, in the setting of protoporphyria, have been associated with reactive oxygen species (ROS) formation and protein aggregation in hepatocytes. Created in https://BioRender.com. Abbreviations: ALAS, δ-aminolevulinate synthase; CPOX, coproporphyrinogen III oxidase; DOVA, 4,5-dioxovaleric acid; ROS, reactive oxygen species; UROS, uroporphyrinogen III synthase.

acids such as tryptophan and homocysteine. Tryptophan 2,3-dioxygenase (TDO2) is a cytosolic heme-protein, highly expressed in the liver, which catalyzes the first and rate-limiting step in the kynurenine pathway.[173] TDO2 inhibition in the liver causes a buildup in plasma tryptophan, with an increase in tryptophan brain uptake.[174] A few decades ago, heme-depletion was shown to dramatically decrease liver TDO2 activity in rats, with increases in brain concentrations of tryptophan, serotonin, and 5-hydroxyindoleacetic acid.[175] However, more recent experiments have reported that disruption in heme biosynthesis results in a dose-dependent increase of TDO2 activity and a reduction of its saturation (holoenzyme/apoenzyme ratio) with a decrease in serotonin levels, an increase in tryptophan, and a dose-dependent inhibition of phosphoenolpyruvatecarboxykinase (PEPCK) activity.[176] Notably, PEPCK plays a key role

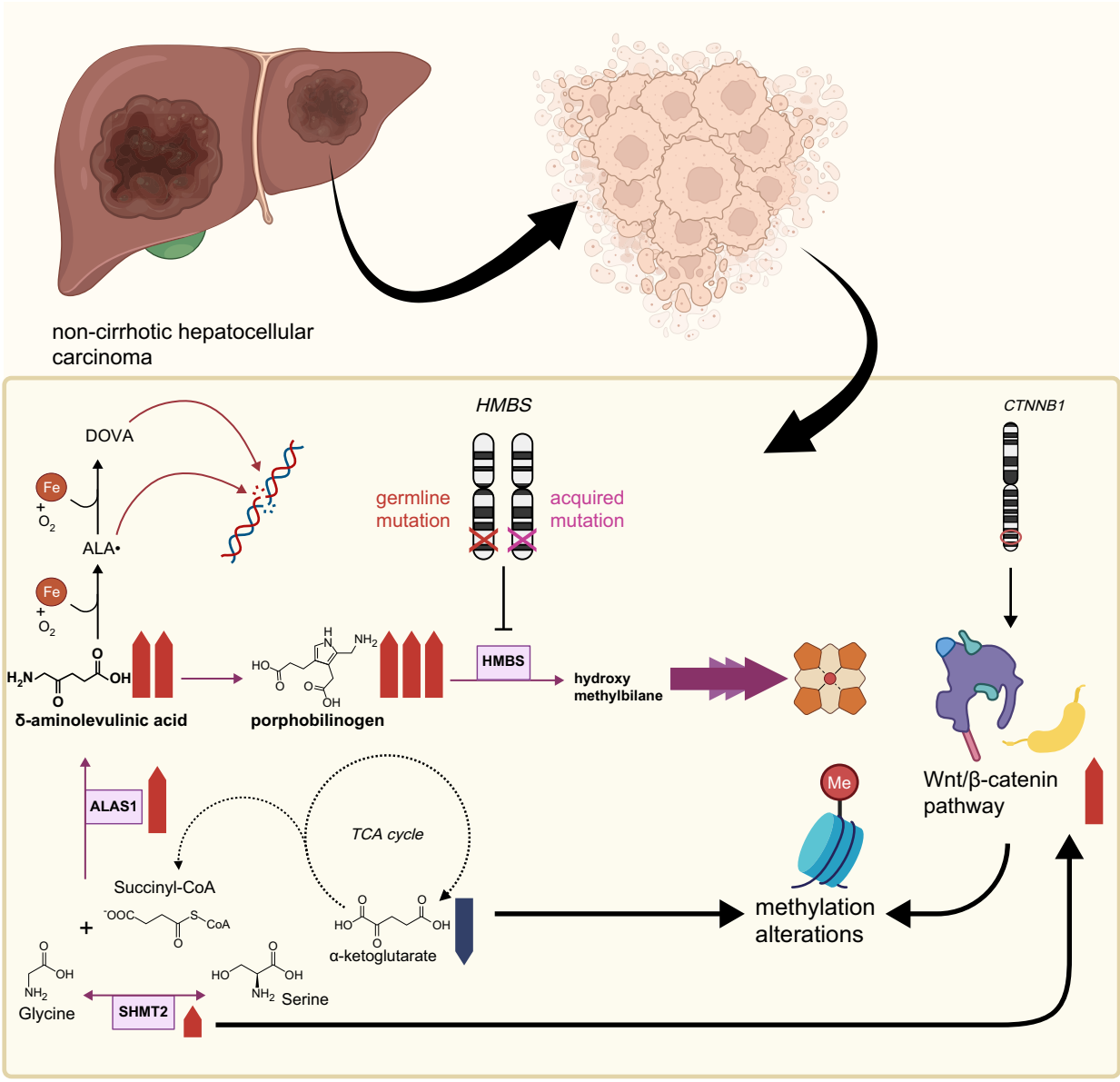

FIGURE 4 Biallelic inactivation of *HMBS* in HCC was associated with massive accumulation of porphobilinogen and, in the presence of activating *CTNNB1* mutations, led to the activation of the Wnt/β -catenin pathway. The subsequent alterations in methylation could be worsened by depletion of α -ketoglutarate, a cofactor for DNA and histone demethylases, due to cataplerosis in the tricarboxylic acid cycle (TCA) triggered by succinyl-coenzyme A, which increased utilization as ALAS1 substrate. Additionally, glycine consumption could enhance the activity of SHMT2, which has also been shown to interact with β-catenin. Created in https://BioRender.com. Abbreviations: ALAS, δ-aminolevulinate synthase; DOVA, 4,5-dioxovaleric acid.

in gluconeogenesis, and its inhibition may contribute to the alterations in the bioenergetic profile, which were noted in several animal models of AHP.[177–179] In this regard, peroxisome proliferator-activated receptor γ coactivator 1α likely represents an important actor connecting ALAS1 induction with nutritional status.[180] Metabolomics studies have supported the hypothesis of TDO2 activation in acute porphyrias, as significant increases in urinary kynurenine and its metabolites were measured in patients with AIP compared to healthy controls.[181] Recently, analyses on urinary and blood metabolomes have also disclosed significant differences in bile acid composition between severely symptomatic patients and those with mild/asymptomatic AIP.[182]

Liver carcinogenesis δ-aminolaevulinic acid could be directly involved in the development of PLC[2,183] (Figures 3 and 4). In the presence of iron and oxygen, ALA undergoes a phosphate-catalyzed autoenolization to yield the oxidizing species superoxide anion (O_2·), HO· radical, and enoyl radical (ALA·).[184,185] Through the production of reactive oxygen species, ALA has been shown to be genotoxic both in vitro and in vivo.[183,186] In a following step, ALA· is oxidized by iron to 4,5-dioxovaleric

acid, a DNA alkylating agent[187] to which guanine moieties are particularly susceptible in the presence of ferritin.[188] In this regard, it has been suggested that bilirubin may have an important detoxifying activity against ALA-induced cell injury.[189] Additionally, ALA-driven oxidative damage alters the permeability of the mitochondrial membrane[190] and ALA administration induced apoptosis on hepatocarcinoma cell lines, possibly through an alteration of the cell cycle regulation by cyclin-dependent kinases; in this setting, hemin and D-glucose administration were able to increase cell survival.[191]

Importantly, primary rat hepatocytes treated with ALA showed a dose-dependent increase in p53 expression, an increase in lipoperoxidation, and an alteration of the expression pattern of proteins related to the oxidative-stress response.[192]

It is also worth noting that type 1 tyrosinemia—an inborn disease in which a defect in tyrosine metabolism leads to succinylacetone-mediated ALAD inhibition and ALA accumulation—if left untreated, is associated with a high incidence of liver damage and HCC.[193]

From a genetic standpoint, a "double hit" hypothesis has been proposed after a biallelic inactivating mutation was detected in the HCC tissue of 2 patients with AHP (one with VP and another with AIP). In these patients, both the germline mutation and an additional somatic mutation in trans (of the *PPOX* or the *HMBS* gene, respectively) were found in the cancerous tissue.[194] Importantly, additional mutations in a set of HCC-related genes were excluded, so that the authors of this study suggested that *PPOX* and *HMBS* could be directly involved, either as oncogenes or as tumor suppressor genes, in the development of HCC. Biallelic inactivation of HMBS was associated with massive accumulation of porphobilinogen and, in the presence of activating *CTNNB1* mutations, led to the activation of the Wnt/β-catenin pathway (Figure 4).

Transcriptomics studies A few studies have investigated the transcriptome of explanted livers of patients with AHPs.[195–197] One of the most recent reports showed an increased expression of *UROS* and heme oxygenase 1, and a decrease in *UROD*, *CPOX*, *PPOX*, and *TDO2* expressions compared to healthy controls[197]—as for *TDO2*, a previous metabolomics study suggested that it should be increased in activity instead.[181] Quite unexpectedly, the expression of *ALAS1* and *HMBS*, as well as some genes involved in inflammation or bioenergetics, did not significantly differ between the porphyric liver and the healthy controls. However, an important factor that may have influenced gene expression in the porphyric liver is that the patient with AIP had received a prophylactic hemin infusion before transplantation, so the observed differences in gene translation should probably be interpreted in the context of further investigations, perhaps on animal models. Instead, a recent transcriptomics study on HepG2 cells revealed several metabolic pathways enriched under ALA treatment, confirming that ALA induces a metabolic reprogramming consistent with its pro-oxidant and carcinogenic effects.[198]

Additional considerations Some speculation about the pathogenic role of the liver in AHPs may result from a comparison between the different kinetics in the hepatic and renal heme biosynthetic pathways.[163,199] Compared to the liver, it has been observed that kidney ALAS1 is somewhat more refractory to induction by porphyrinogenic stimuli,[199] with kinetics of hours instead of minutes. At the same time, heme administration promptly inhibits kidney ALAS1 activity, as in the liver isoform. Furthermore, the ratio of ferrochelatase-to-ALAS1 activity seems higher in renal than liver cells. These lines of evidence, among others, have suggested that the kidney may have a higher content of "free," unbound heme with intracellular regulatory functions, which may serve as a protective buffer to acute heme-depleting triggers.[199] By contrast, it could be hypothesized that the liver may suffer from a basally "low" concentration of intracellular-bound heme, which would make it more susceptible to ALAS induction (and overproduction of toxic heme precursors) in the presence of porphyrinogenic stimuli. An estimation of the amount of unbound heme pool reserves in hepatocytes, as well as other functional studies, would be instrumental to either corroborate or dismiss this hypothesis.[163]

Clinical pearls for the hepatologist

Principles of management While being primarily involved in the pathogenesis of AHPs, the liver is also a target of damage. Liver manifestations can be subtle, since it should be remarked that sometimes an isolated increase in liver enzymes can be an early hallmark of AHPs.[200–204] For example, a retrospective study in Sweden reported that patients with manifest AIP presented with higher alanine aminotransferase and bile acid levels, compared to asymptomatic carriers of *HMBS* mutations.[201] Furthermore, in the phase 3 trial with givosiran (see below), a significant minority of patients with recurrent acute attacks had baseline increased serum aminotransferases,[204] although the impact of cofactors such as therapy with hemin infusions has not been determined.[203] Therefore, AHP should be considered in cases of unexplained hypertransaminasemia, after other more common causes have been ruled out. Furthermore, an elevation in serum aminotransferases usually accompanies the onset of APAs.

Correctly recognizing an APA is paramount, particularly in patients presenting with the disease for the first time, to allow the prompt initiation of potentially life-

saving treatment. If an APA is suspected, reference centers should be contacted as soon as possible to confirm the diagnosis and initiate treatment. At the same time, not all abdominal, gastrointestinal, or neurological episodes in a known patient with AHP should be hastily attributed to porphyria, as these patients are equally at risk of developing other, more common diseases as the general population.

All environmental exposures known to trigger APAs, such as porphyrinogenic drugs (an up-to-date database of safe and unsafe medications can be found in the study NAPOS[205]), infections or other health issues not properly managed, fasting or decreased calorie intake, smoking, and alcohol use should be eliminated during an attack, and minimized to prevent future attacks.[162]

Therapeutic approach

Hemin infusion Consistent with the physiopathology of the disease, APAs are effectively managed with infusions of heme arginate (hemin), which downregulate ALAS1 through a negative feedback and stop the buildup of ALA.[162] The prophylactic management of patients with frequent or markedly severe APAs has always been suboptimal, since until recently the main therapeutic option was represented by periodic, off-label hemin infusions. Clinicians should be aware that patients with AHP treated with prophylactic heme arginate (ie, in countries with no immediate access to givosiran) are at risk of developing liver iron overload and fibrosis,[206,207] as a 10 mL-vial of heme arginate contains 250 mg human hemin and 22.7 mg of iron.[4] In this setting, therapy with phlebotomy or iron chelators could be considered, although the former is often poorly tolerated,[206] and the risks of chelation-associated adverse events (including cytopenia, kidney impairment, hearing and visual disturbances, and liver disease) should not be neglected.[208]

Givosiran In the last few years, a novel small intefering RNA (siRNA)-based therapeutic has revolutionized the management of AHPs.[204,209] Givosiran exploits the intracellular RNA-induced silencing complex (RISC) machinery to inhibit ALAS1 translation, specifically targeting hepatocytes through a triantennary N-acetylgalactosamine (GalNac) moiety, which binds to asialoglycoprotein receptors. In the phase 3 trial and long-term follow-ups, givosiran resulted very effective in lowering the annualized APAs rate and in improving the patients' quality of life,[210], indirectly confirming the hypothesis that the porphyric liver is the main culprit for causing the systemic disease.

Quite unexpectedly, moderate-to-severe hyperhomocysteinemia has been detected in patients treated with givosiran,[211–215] although in most cases, homocysteine levels regressed to normal or near normal with vitamin B6 supplementation therapy. As high levels of plasma homocysteine are associated with an increased risk of thromboembolic events and therapy with givosiran is long-term, special care is required to monitor for the occurrence or worsening of hyperhomocysteinemia in givosiran-treated patients.[210] In patients treated with givosiran, hypertransaminasemia is a common adverse event.[204,209,216] In most cases, the alterations of liver enzymes are mild and not clinically significant, so they do not justify a suspension of siRNA therapy.Worthy of note, the first case of a patient who developed DILI after givosiran administration has been recently reported; the authors of the communication recommended close monitoring for DILI or other adverse reactions under givosiran, for at least a few months after starting therapy and periodically thereafter.[217]

Liver transplantation Corroborating the hypothesis that the liver is the primary site of the disease, liver transplantation is curative in AHPs,[218] since it unburdens patients from the threat of APAs and sometimes relieves them from chronic neurological symptoms. Conversely, APAs have been reported in patients who received liver grafts from donors affected by AHPs in the course of "domino" liver transplantations.[219] Be that as it may, transplantation is reserved only to those patient who do not benefit from any other therapeutic option.[220] To date, a single case of liver transplantation in a patient with Doss disease has been reported,[164] whereas almost all others have been performed in patients with AIP.[207]

Primary liver cancer in AHPs Patients with AHPs have long been known to be at increased risk of developing noncirrhotic primary liver cancer (PLC—mainly HCC, but also cholangiocarcinoma).[69,221–230] Case series have focused mainly on populations of patients with AIP,[69,221,226,231] in whom the association with HCC was first proposed by Lithner and Wetterberg.[222] However, some reports in patients with VP or HCP have also been published.[226,232–234] Contrary to the epidemiology of liver cancer from other causes, a higher prevalence of PLC in AHP women has been reported, with low rates of liver fibrosis or other classical risk factors associated with HCC.[228]

In this regard, it is of great interest the discovery of a distinct subset of sporadic HCC with a biallelic *HMBS* mutation.[235,236] Intriguingly, nonporphyric patients with this HCC genotype were predominantly female without liver fibrosis or the classical HCC risk factors.

Importantly, in some patients, HCC was discovered before they showed any other symptom of AHP, even

though the largest cohort assembled to date has recently highlighted a strong correlation between PLC and AHP activity[231,237] In this regard, some authors have suggested that a screening for AHP should be made in those patients presenting with HCC in the absence of the most commonly associated risk factors (hepatotropic virus infection, cirrhosis, alcoholic hepatopathy, metabolic dysfunction–associated steatotic liver disease).[234]

Be that as it may, surveillance for PLC in patients with AHP is warranted: it has been proposed that biannual liver cancer screening should be undertaken at least in all patients with a history of either symptomatic disease or biochemical activity after age 50. It is still a matter of debate whether to extend these recommendations to biochemically inactive patients.[207,216]

CONCLUSIONS

Although porphyrias present under strikingly diverse clinical pictures, all of them share a certain degree of hepatic involvement, from isolated hypertransaminasemia up to life-threatening conditions such as cirrhosis, acute organ failure, and cancer. Furthermore, hepatologists should be aware that porphyrias can have severe (even fatal) acute extrahepatic complications, whose triggers (eg, medications) should be avoided. In this review, we have outlined the main lines of evidence concerning the role of the liver in the pathogenesis and clinical manifestations of these rare diseases. Furthermore, we have highlighted the main clinical clues to which hepatologists should pay attention, as liver-related issues are being increasingly recognized as a central aspect of the clinical management in all forms of porphyria. Accordingly, a multidisciplinary team dealing with porphyrias should always include an expert in liver diseases.

Given their utmost rarity, porphyrias do represent a diagnostic challenge for the clinician. At the same time, confirmation of a disease-specific biochemical alteration is quite straightforward and not very expensive. Since the treatment is often very specific and can effectively improve the symptoms, overall quality of life, and even life expectancy in some cases, it is of paramount importance to correctly and promptly recognize a patient with porphyria. Hepatologists should be aware of porphyrias as a differential diagnosis for unexplained liver alterations or liver disease with atypical presentation. In order to minimize the risk of a misdiagnosis, local reference centers should be addressed for consultancy whenever one of these rare diseases is suspected. This can be possible, though, only if appropriate clinical awareness is spread among clinicians dealing with liver or metabolism-related diseases.

CONFLICTS OF INTEREST

Authors: Andrea Ricci has received support to attend meetings from Alnylam Pharmaceuticals. Paolo Ventura has received consulting fees, support to attend meetings, and honoraria from Alnylam Pharmaceuticals and Recordati Rare Diseases, and has participated in an Advisory Board for Alnylam Pharmaceuticals. Contributor: Matteo Marcacci has received consulting fees, support to attend meetings, and honoraria from Alnylam Pharmaceuticals and Recordati Rare Diseases, and has participated in an Advisory Board for Alnylam Pharmaceuticals. The remaining authors have no conflicts to report.

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