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Liver Transplantation in the Management of Porphyria

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Abstract

Porphyrias are a group of eight metabolic disorders, each resulting from a mutation that affects an enzyme of the heme biosynthetic pathway. Porphyrias are classified as hepatic or erythropoietic, depending upon the site where the gene defect is predominantly expressed. Clinical phenotypes are classified as follows: (1) acute porphyrias with neurovisceral symptoms: acute intermittent porphyria; delta amino-levulinic acid hydratase deficiency porphyria; hereditary coproporphyria; and variegate porphyria and (2) cutaneous porphyrias with skin blistering and photosensitivity: porphyria cutanea tarda; congenital erythropoietic porphyria; hepatoerythropoietic porphyria and both erythropoietic protoporphyrias: autosomal dominant and X-linked. Liver transplantation (LT) may be needed for recurrent and/or life-threatening acute attack in acute intermittent porphyria or acute liver failure or end-stage chronic liver disease in erythropoietic protoporphyria. LT in acute intermittent porphyria is curative. Erythropoietic protoporphyria patients needing LT should be considered for bone marrow transplantation to achieve cure.

Conclusion—This article provides an overview of porphyria with diagnostic approaches and management strategies for specific porphyrias and recommendations for LT with indications, pretransplant evaluation, and posttransplant management.

The principal sites of heme biosynthesis are liver and bone marrow, where production occurs of cytochrome P450 (CYP) enzymes and hemoglobin, respectively. The heme biosynthetic pathway is an eight-step pathway, with each step catalyzed by a specific enzyme. Porphyrias is a group of disorders with each specific porphyria resulting from mutations in one of eight genes encoding enzymes of the heme biosynthetic pathway (Fig. 1). They are classified based on the site of genetic defect expression as erythropoietic, including erythropoietic protoporphyria (EPP) and congenital erythropoietic porphyria (CEP), or hepatic, including porphyria cutanea tarda (PCT), acute intermittent porphyria (AIP), delta-aminolevulinic acid (ALA) deficiency porphyria (ADP), hereditary

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coproporphyria (HCP), variegate porphyria (VP), and hepatoerythropoietic porphyria (HEP; Table 1). In all porphyria but one, the mutation causes loss of function of the gene product (Table 1). An exception is a gain-of-function mutation in the ALA synthase 2 gene (*ALAS2*; the erythroid-specific form of the enzyme) that leads to excess production of protoporphyrin (PP) IX.¹

Diagnostic Approach to Porphyria

Acute Neurovisceral Symptoms

Diagnosis of porphyria as a cause of acute abdominal pain is often delayed with repeated visits to the emergency room and performance of multiple expensive tests. Diagnostic approach to porphyria will be discussed briefly and details may be referred to more extensive reviews.^{2,3} The initial screening test for suspected acute porphyria is spot urine testing for porphobilinogen (PBG). The Watson Schwartz test detects urinary PBG, but lacks sensitivity and cannot quantify PBG levels.³ A commercially available Trace PBG kit (Thermo Scientific, Waltham, MA) provides semiquantitative estimation of PBG in a spot urine sample.³ A normal urinary PBG level (0-4 mg/L) at the time of acute symptoms rules out acute porphyria. Further diagnosis of specific acute porphyria is established with analysis of urine, plasma, and feces for quantitative determination of ALA, PBG, and porphyrins. Genetic testing may be performed to identify the genetic mutation in the patient and screening for asymptomatic relatives of the proband case.

Cutaneous Symptoms

Skin lesions and photosensitivity are characteristic symptoms of cutaneous porphyrias. Elevation of plasma porphyrins (normal, <0.9 µg/dL) differentiates cutaneous porphyrias from pseudoporphyria, a nonporphyric condition with skin lesions caused by certain drugs. Estimation of total and fractionated porphyrins in plasma, urine, red blood cells (RBCs), and feces establishes diagnosis of specific cutaneous porphyria.

Liver Transplantation in Porphyria

The rationale for liver transplantation (LT) in porphyria is to treat liver disease as a complication of porphyria, such as in EPP, or to correct genetic defects for intractable neurovisceral symptoms, such as in AIP. PCT is readily treatable by phlebotomy or low-dose hydroxychloroquine, and LT may be needed for liver disease secondary to concomitant alcohol abuse or hepatitis C.⁴ LT is not effective for CEP.

LT in EPP

EPP, the third-most common porphyria after PCT and AIP, occurs as a result of decreased activity of ferrochelatase (FECH) from combination of an inactivating mutation affecting one *FECH* allele, and an intronic polymorphism (IVS3-48c) affecting splicing of other allele and produces nonfunctional FECH messenger RNA.⁵⁻⁷ Approximately 4%-10% of EPP cases are the result of X-linked gain-of-function mutation of the *ALAS2* gene on the chromosome, Xp11.2.^{1,8} Both X-linked and autosomal recessive EPP are characterized by increase in PP levels with nonblistering photosensitivity beginning in early childhood.⁹

Rationale for LT in EPP

Some EPP patients develop end-stage liver disease secondary to PP-induced liver damage and need LT as a life-saving measure. However, the genetic defect in EPP is expressed in erythroid cells, where LT will not correct enzyme deficiency. The main source of PP in EPP is erythroid cells with increase in plasma concentration as PP diffuses out of RBCs. Water-insoluble PP is taken up by hepatocytes and excreted in bile. Increased biliary concentration of PP changes the bile concentration of phospholipids and bile acids, leading to cytotoxic bile.^{10,11}

PP crystal deposits with structural changes in hepatocytes and bile ducts (Fig. 2A) have been shown in the absence of clinical liver disease.¹² PP-induced damage to hepatocytes and bile ducts may lead to hepatobiliary disease in up to 41% of patients.⁹ EPP crisis characterized by sudden, marked increase in PP levels, severe abdominal and back pain, and severe liver disease with acute liver failure and/or neurologic dysfunction may occur in approximately 3%-5% of EPP patients.⁹ EPP patients are also prone to development of cholelithiasis and choledocholithiasis, with biliary PP acting as the nidus for stone formation.⁹

Surveillance for and Diagnosis of Liver Disease in EPP

In spite of the known association of EPP with severe liver disease, its predictors remain unclear. It is suggested that patients with autosomal recessive, X-linked, or null mutation EPP and those with family history of EPP-related liver disease may be prone to this complication.^{6,9,13-15} Comorbid conditions, such as alcohol abuse, viral hepatitis, and use of hepatotoxic drugs, may also contribute to hepatic disease.¹⁶ In one study, PP levels in RBC were higher among patients with liver disease, compared to those without liver disease ($2,134 \pm 450$ vs. 730 ± 112 $\mu\text{g/dL}$; $P < 0.001$).¹⁷ It is suggested that risk of liver disease may be high with elevation of PP in RBCs above 1,500-2,000 $\mu\text{g/dL}$ (normal, 20-80 $\mu\text{g/dL}$) or plasma PP above 50 $\mu\text{g/dL}$ (normal, <0.9 $\mu\text{g/dL}$).¹⁸ Estimation of urine coproporphyrin fractions has shown higher proportion of isomer 1 (43%-91%; normal, $<31\%$) in patients with hepatobiliary complications.¹⁷

With lack of predictors of EPP liver disease, physicians have followed PP levels in RBCs and liver chemistry at 6- to 12-month intervals.^{9,18,19} However, sensitivity of abnormal liver chemistry in diagnosing EPP-related liver disease remains unclear.⁹ The gold standard for diagnosis of liver disease in EPP patients is liver biopsy and the cardinal feature is intrahepatic cholestasis with relative lack of portal and lobular inflammation. Special staining, immunofluorescence, and polarization microscopy will demonstrate deposition of PP birefringent crystals in the hepatocytes (Fig. 2B-F).^{12,20,21}

Pretransplant Evaluation and Experience in LT for EPP

The first LT for EPP liver disease was reported in 1980, with the patient dying at 4 weeks from disseminated candidiasis.²² Since then, in the literature, 62 transplants (23 in the United States, 35 in Europe, and 4 from Asia) have been performed in 50 EPP cases (mean age of 39 years From the United States and 31 years from Europe; 60% males; median Model for End-Stage Liver Disease score: 21).^{16,23} EPP patients needing LT do not receive exception points or status 1A; however, an appeal may be made on a case-by-case basis. Six

cases in the U.S. series were in the pediatric age range. Most LTs in EPP have been done using deceased donors, except for 2 cases in Europe and 2 in Japan.²⁴

Probably, before transplant, it is important to lower porphyrin levels to prevent light induced skin and tissue burns during surgery, posttransplant neuropathy, and recurrence of EPP liver disease in allograft. Effective measures include suppression of porphyrin accumulation by (1) intravenous (IV) hemin (Panhematin in the United States and heme arginate in other countries),^{25,26} (2) filtering and removing porphyrins by plasma or RBC exchange,²⁶ and (3) increasing excretion of porphyrins with ursodeoxycholic acid (UDCA) and cholestyramine.⁹ Approximately half of LTs (12 from the United States and 17 in Europe) required pretransplant measures for either EPP crises or acute liver failure.

Multiple sessions of plasma exchange (plasmapheresis), in combination with IV hemin, is commonly used with RBC exchange reserved for refractory cases.⁹ Plasmapheresis may be advantageous in removal of bile acids with improvement in pruritus.²⁶ Plasma PP decrease is followed by reduction of PP levels in RBCs.²⁷ However, efficacy of improvement in liver disease is unpredictable. It is suggested that PP levels be reduced below 5,000 $\mu\text{g/dL}$ in RBCs and below 50 $\mu\text{g/dL}$ in plasma.²⁶ Pretransplant treatment was effective in reducing mean bilirubin from 9.5 to 5.9 mg/dL and PP levels in RBC from 6,281 to 2,301 $\mu\text{g/dL}$.¹⁶

Cholestyramine binds PP and excretes them in feces without effect on RBCs and plasma PP levels.²⁸ Bile acids, including UDCA, have not been shown to be of clear benefit.^{17,29} Extracorporeal albumin dialysis seemed better than plasmapheresis at removing circulating PP and may be an option for patients with EPP crises who are refractory to other measures.³⁰

Issues During Surgery and Posttransplant Follow-up

EPP patients are prone to skin and tissue burns during LT because of activation of PP by light in the blue-violet region around 400 nm. TA-81 (Madico Inc., Woburn, MA) and 61011 (Reflectiv SA, Cretil, France) filters block light below the 470-nm wavelength and provides complete protection from phototoxic injury without visual distortion during the operation. The CLS-200-X filter provides partial protection from wavelengths below 400 nm.^{31,32} In transplants performed without special filters, one case each from the United States and Europe developed grade 3 intestinal burns and died from sepsis as a result of bowel perforations.^{16,23} EPP patients without liver disease have successfully undergone procedures including endoscopies and prolonged cardiac surgery, provided PP levels are monitored.^{31,33}

Patients with EPP may develop neurological dysfunction before or after LT and present with proximal motor weakness that may progress to respiratory paralysis requiring mechanical ventilation.³⁴ This is frequently associated with hypertension, tachycardia, abdominal pain, nausea, vomiting, and constipation.³⁴ Electromyogram shows axonal denervation without demyelination.³⁵ Among LTs in EPP, 14 patients (6 in the U.S. series) had neuropathy, which necessitated prolonged mechanical ventilation in 5.^{16,23}

Biliary complications reported in approximately 45% of patients included anastomotic strictures in 5, choledocholithiasis in 2, biliary leak in 1, and displaced T tube in 1.¹⁶ These details were not available from the European study.²³ An immunosuppression regimen with cyclosporine or tacrolimus, in combination with azathioprine, steroids, or mycophenolate mofetil, was safe.^{16,23}

Because LT does not correct genetic defects in bone marrow, recurrence of EPP liver disease is a potential problem.²³ Retransplantation was needed in 3 U.S. patients with recurrent EPP and 4 European patients (1 recurrent EPP, 2 rejection, and 1 unknown cause).^{16,23} A total of 6 cases (3 in the United States, 2 in Europe, and 1 in Japan) died within 2 months of LT: 4 from sepsis, 1 from primary graft nonfunction, and 1 from multiorgan failure.³⁶ Posttransplant survival ranges from 47% to 66% at 10-year follow-up.

Bone Marrow Transplantation in EPP

Indications for bone marrow transplantation (BMT) in EPP are complex, because predictors of liver disease development in EPP are lacking.³⁷ BMT after LT cures EPP and thus would prevent recurrent disease in the allograft, but its timing remains unclear. A 9-year-old boy who received BMT within 4 months of LT for EPP-related liver disease suffered from delayed immune recovery, causing zoster virus reactivation and death.³⁸ In another case, sequential LT and BMT were performed in a 15-year-old boy with BMT performed 6 months after LT.³² The patient required splenectomy and a second BMT to maintain engraftment at 5 and 7 months, respectively, after the first BMT. In patients who recover from liver disease and have minimal or no fibrosis, BMT may be done without need for LT to cure the EPP (Fig. 3).³⁹

LT in Hepatic Porphryia

Hepatic porphyria can present with (1) acute neurovisceral symptoms (AIP and ADP), (2) blistering skin lesions (PCT and HEP), or (3) both cutaneous and neurovisceral symptoms (VP and HCP).

AIP

Of all hepatic porphyrias, LT has been used most for AIP, an autosomal dominant disease resulting from mutation of the *PBG deaminase* gene. Recurrent neurovisceral attacks are common in women after puberty and include abdominal pain with peripheral and autonomic neuropathy. Mental symptoms include insomnia, anxiety, restlessness, disorientation, paranoia, and hallucinations. Hyponatremia, encephalopathy, seizures, and tremors may occur.^{2,3} The mechanism of neuropathy is unclear, but may be caused by ALA and/or heme deficiency. Skin lesions are not a feature of AIP.

Rationale for LT in AIP

AIP is a result of deficiency of the *PBG deaminase* enzyme, resulting in accumulation of porphyrin precursors. LT in AIP corrects the genetic defect in the liver and restores normal levels of PBG and ALA with resolution of symptoms.

Acute AIP Attack—IV hemin at a dose of 3–4 mg/kg is the treatment of choice for acute attack.² Higher doses may be associated with hepatic and renal failure.^{40,41} Lyophilized heme may be reconstituted with 20% human serum albumin and infused through a central vein to prevent phlebitis resulting from anticoagulant effects of heme degradation products.²

Since its first use in 1971,⁴² many reports have described benefits of hemin in controlling acute attack.^{43,44} In a double-blind, randomized, placebo-controlled trial on 24 AIP patients, hemin was better, compared to placebo, in normalizing biochemical parameters with a trend toward benefits in pain control, need for analgesics, and hospital stay.⁴⁴ In a large, open-label study on 111 patients with 305 acute attacks, hemin was effective in controlling acute attack in 73% of cases.⁴³ IV dextrose and normal saline are used to prevent hypoglycemia and hyponatremia.³ LT is considered for life-threatening acute attack of AIP or progression despite hemin therapy.

Chronic Recurrent Attacks—There are no clear predictors to identify patients at risk for frequent recurrent attacks. In an open-label study on 40 AIP patients with recurrent attacks, prophylactic hemin infusion (3–4 mg/kg) given once every 1–2 weeks prevented further attacks in 68% cases.⁴³ Some women experience frequent attacks during the last half of the menstrual cycle, and use of gonadotropin-releasing hormone analogs may help these patients.^{2,45} LT is considered for patients with frequent acute attacks who are unresponsive to pharmacological approach.

Pretransplant Evaluation and Experience in the Use of LT in AIP

The first LT for AIP, performed in 2002 in a 19-year-old woman with severe frequent neurovisceral attacks, successfully cured AIP.⁴⁶ Recently, a retrospective study from the UK reported on the experience of LT in 10 patients (median age: 31 [range, 18–50] years; 9 females) with AIP and recurrent neurovisceral attacks and poor quality of life.⁴⁷ Clinical and biochemical remission occurred in all patients, with PBG and ALA levels returning to normal within 24–72 hours.⁴⁷ AIP patients needing LT do not receive exception points, but an appeal may be made on a case-by-case basis. Although none of the LTs in AIP patients have been performed with concomitant hepatocellular carcinoma (HCC), it is recommended to screen AIP patients above the age of 50 years for HCC using ultrasound examination at a 6- to 12-month interval.

LT for patients with severe acute attacks requiring prolonged mechanical ventilation have been done, but outcomes are better when patients have recovered from respiratory failure.⁴⁸ Although LT corrects enzyme defects in the liver and prevents further attacks, recovery of pretransplant neurological deficit is unpredictable. Therefore, a detailed neurological evaluation by a specialist should be obtained to assess pretransplant neurological status. Ideally, LT should be performed before the onset of permanent neurological damage. However, predictors of neurological damage remain unclear.

Repeated use of hemin infusions before LT may lead to iron overload and venous thrombosis. This may affect the ability to administer hemin transfusions as well as transplant surgery if the femoral veins are unavailable to crossclamp the inferior vena cava during surgery.^{2,48} Drugs metabolized through the CYP pathway with potential for precipitation of

all acute porphyria, including AIP, should be avoided. A complete updated list of safe and unsafe drugs is available online (www.drugs-porphyria.org).

Patients with AIP are prone to develop renal dysfunction resulting from associated hypertension.^{49,50} Simultaneous liver kidney transplantation is reported in 2 AIP patients with renal dysfunction requiring chronic hemodialysis.⁵¹

Issues During Surgery and Posttransplant Follow-up in AIP

Of 14 reported LTs in AIP,^{40,46,47,51} complications have included hemorrhage (n = 2), bile leak (n = 1), renal dysfunction (n = 2), and hepatic artery thrombosis (n = 4).⁴⁷ After a median follow-up of 23.4 (range, 3.2-109) months, 2 patients died at 3 and at 26 months from multiorgan failure.⁴⁷ Survival rates were similar to transplantation for other indications, with 93% and 77% at 3 months and 5 years, respectively.⁴⁷ Usually, explant is normal, except for siderosis in 7 of 10 explants resulting from chronic use of hemin therapy.^{47,52} None had preexistent or incidental HCC.

Hereditary Coproporphyria, Variegate Porphyria, and ALA Dehydratase Deficiency Porphyria

Although, genetically and biochemically distinct, HCP and VP share many features with AIP. As with AIP, they are autosomal dominant diseases with low penetrance.⁵³ HCP is the result of mutation of coproporphyrinogen oxidase that catalyzes the conversion of coproporphyrinogen III to PP.⁵⁴ VP is the result of mutation of protoporphyrinogen oxidase, an enzyme mediating conversion of protoporphyrinogen IX to PP (Fig. 1). Patients with HCP and VP experience neurovisceral attacks similar to those observed in patients with AIP, but, in contrast to AIP, blistering skin lesion may be observed in patients with VP and, less commonly, in patients with HCP.⁵³ As is the case with AIP, chronic hypertension, renal disease, and incidence of HCC are increased in patients with VP and HCP. Management of acute attacks is the same as for AIP, with supportive care and hemin infusion being the cornerstone of treatment. Although the dermal manifestations of VP and HCP are similar to those of PCT, phlebotomy or low-dose chloroquine or hydroxychloroquine, which are highly effective in resolving the blistering photosensitivity of PCT, are ineffective in HCP and VP.⁵³ Therefore, avoidance of sunlight exposure remains the mainstay of management.

No case for LT has been described in HCP, and 1 case has been described in VP. A 46-year-old male patient is described in the literature with VP undergoing transplantation for alcohol-related decompensated cirrhosis. The patient remains well at 3 months with complete normalization of biochemical porphyrin parameters.⁵⁵

ADP, an autosomal recessive disease resulting from deficiency of ALA dehydratase enzyme, is the least common porphyria, with only 6 cases described with confirmed genetic or molecular defect.⁵⁶ LT was performed for a 7-year-old boy with ADP who had severe frequent acute porphyria attacks. Although the patient remained well with less-frequent hospitalizations, abnormal biochemistry persisted.⁵⁷ The patient ultimately died at 2 years and 9 months after LT.⁵⁸

Summary and Recommendations

Porphyrias are a group of metabolic disorders with eight specific porphyrias, each the result of deficient enzyme in the heme biosynthetic pathway. The predominant genetic defect lies either within the bone marrow (erythropoietic porphyria) or liver (hepatic porphyrias). Clinical manifestations include photosensitivity with or without skin lesions (cutaneous porphyrias) or acute neurovisceral symptoms (acute hepatic porphyrias). Most of the experience in LT for the management of porphyria is among patients with EPP and in AIP.

Management of EPP patients includes treatment of photosensitivity with regular monitoring of liver chemistry and erythrocyte and plasma protoporphyrin measurements.⁹ When liver disease is suspected, workup for additional causes of liver diseases should be performed, including alcohol and hepatotoxic drugs, viral hepatitis markers, ultrasound examination, and cholangiogram, if needed. Liver biopsy is recommended in the setting of abnormal liver chemistry, presence of other risk factors for liver disease, or sudden increase in PP levels and/or photosensitivity. It may also be considered for patients with ALAS2 mutations, autosomal recessive EPP, and family history of EPP liver disease.^{9,17} Patients with EPP-related acute liver failure or progressive liver disease should be considered for LT with an expedited referral to centers with expertise in managing porphyria patients. Hemin infusions and/or plasmapheresis should be used to lower protoporphyrin levels for managing the liver disease as well as to improve the posttransplant outcomes in case of a need for LT.^{16,23} Patients who recover from liver crisis and have no or mild fibrosis (stage 0-1) may be referred for evaluation of BMT for cure of EPP.³⁹ Special filters should be used on the operating room lights to protect patients from protoporphyrin-induced skin and tissue burns.³¹ Nontransplant surgery or endoscopic procedures may be safely done in a noncholestatic patient.^{31,33} Sequential BMT should be considered to prevent posttransplant EPP recurrence.³⁷

Management of AIP patients includes management of acute attack with IV hemin infusion, avoiding unsafe drugs with potential for precipitation of acute attack, and annual ultrasound examination for HCC screening among patients > 50 years.^{2,3,44,59} Repeated hemin infusions at 1- to 2-week intervals can be used for prevention of recurrent acute attacks with gonadotropin-releasing hormone analogs as an option for women in childbearing age.^{2,45} LT, an option for patients with severe life-threatening acute attack or for patients with disabling recurrent attacks should be considered before onset of permanent neurological damage.⁴⁷ Evaluation of venous access by ultrasound or venogram (magnetic resonance or computed tomography) is recommended to map out available veins for use in the perioperative period.^{2,48} Given a reported high risk for hepatic artery thrombosis, one should consider anticoagulation after LT.⁴⁷

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Abbreviations

ADP	ALA deficiency porphyria
AIP	acute intermittent porphyria
ALA	delta-amino-levulinic acid
ALAS2	ALA synthase 2 gene
BMT	bone marrow transplantation
CYP	cytochrome P450
CEP	congenital erythropoietic porphyria
EPP	erythropoietic protoporphyria
FECH	ferrochelatase
HCC	hepatocellular carcinoma
HCP	hereditary coproporphyria
HEP	hepatoerythropoietic porphyria
IV	intravenous
LT	liver transplantation
PBG	porphobilinogen
PCT	porphyria cutanea tarda
PP	protoporphyrin
RBCs	red blood cells
UDCA	urodeoxycholic acid
VP	variegate porphyria

Fig. 1.

The heme biosynthetic pathway. Reactions shown above the dashed line take place in the mitochondrion, whereas those below this line occur in the cytosol. At every step of the pathway, corresponding porphyria from the respective deficient enzyme is mentioned in italics and in rectangles. ALAS, aminolevulinic acid synthase; EPP, erythropoietic protoporphyria; ALAD, ALA dehydratase; ADP, ALAD-deficient porphyria; PBGD, porphobilinogen deaminase; AIP, acute intermittent porphyria; UROS, uroporphyrinogen III synthase; CEP, congenital erythropoietic porphyria; UROD, uroporphyrinogen III decarboxylase; PCT, porphyria cutanea tarda; CPO, coproporphyrinogen oxidase; HCP, hereditary coproporphyria; PPO, protoporphyrinogen oxidase; VP, variegate porphyria; FECH, ferrochelatase. Hepatoerythropoietic porphyria is the result of autosomal recessive UROD mutation with severe deficiency of UROD in liver and RBCs and causes the same phenotype as PCT with onset of disease in childhood. *ALAS, rate-limiting enzyme in heme biosynthesis has 2 isoforms: ALAS-1 is the general form present in all cells, and ALAS2 is the erythroid-specific variant present only in RBCs. †X-linked EPP is caused by a gain-of-function mutation in ALAS2. EPP is also caused by mutations in FECH.

Fig. 2.

Liver biopsy in erythropoietic protoporphyria. (A) Early bile duct damage with cholestasis (arrow). (B) Cholestasis with pigment deposits (arrows) within hepatocytes. (C) Red fluorescence in hepatocytes (arrow), as demonstrated by fluorescence microscopy crystals. (D) Birferigence of pigment deposits, as demonstrated by polarization microscopy, showing protoporphyrin crystals (arrows) in a maltese cross shape. (E) Same polarization microscopy but with birefringent crystals in an unstained specimen. (F) Explant from a patient with EPP showing a black liver.

Fig. 3.

Suggested approach to management of protoporphyric hepatopathy in a patient with erythropoietic protoporphyria. *Severe disease: liver disease with worsening liver enzymes and/or bilirubin or development of liver failure.

Overview of Porphyrria

Table 1

Affected Enzyme		Inheritance Pattern	Nonblistering Photosensitivity	Blistering Photosensitivity	Acute Neurovisceral Symptoms
Erythropoietic					
Erythropoietic protoporphyria (X-linked)	delta-Aminolevulinic acid synthase 2 * (<i>ALAS2</i> ; erythroid specific)	X-linked	Y	N	N
Erythropoietic protoporphyria (autosomal)	Ferrochelatase (<i>FECHE</i>)	Autosomal recessive	Y	N	N
Congenital erythropoietic porphyria	Uroporphyrinogen synthase (<i>UROS</i>)	Autosomal recessive	Y	Y	N
Hepatic					
delta-Aminolevulinic acid dehydratase porphyria	delta-Aminolevulinic acid dehydratase (<i>ALAD</i>)	Autosomal recessive	N	N	Y
Acute intermittent porphyria	Prophobilinogen deaminase (<i>PBGD</i>)	Autosomal dominant	N	N	Y
Hereditary coproporphyria	Coproporphyrinogen oxidase (<i>CPO</i>)	Autosomal dominant	Y	Y	Y
Variegate porphyria	Protoporphyrinogen oxidase (<i>PPO</i>)	Autosomal dominant	Y	Y	Y
Porphyria cutanea tarda [‡]	Uroporphyrinogen decarboxylase (<i>UROD</i>)	Autosomal dominant	Y	Y	N
HEP	Uroporphyrinogen decarboxylase	Autosomal recessive	Y	Y	N

All autosomal dominant porphyria have low penetrance.

* Gain-of-function mutation of *ALAS2* causes X-linked erythropoietic protoporphyria.

[‡] Most cases (~80%) of porphyria cutanea tarda are sporadic or type I (no *UROD* mutation) because of an acquired inhibitor of *UROD*, but heterozygosity for mutant *UROD* predisposes to PCT in familial or type II disease.