REVIEW

Liver Transplantation for Porphyria: Who, When, and How?

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Porphyrias are a heterogenous group of diseases that may result in disabling or life threatening neurovisceral symptoms and/or cutaneous photosensitivity. In acute intermittent porphyria, the clinical features, particularly neurological symptoms, may be life-threatening and disabling. Conventional treatment with human hemin, though effective in reducing symptoms, does not reverse neuropathy when structural nerve damage has occurred and may cause intense phlebitis. Liver transplantation (LT) may be considered as treatment for those with repeated life-threatening acute attacks resulting in poor quality of life, requirement of ventilatory support, and progressive loss of venous access due to hemin infusion. Patients with variegate porphyria (VP) present after puberty with neurovisceral symptoms and skin manifestations. LT resolved VP in the 1 patient reported in the literature. Aminolaevulinic acid dehydratase deficient porphyria is a rare autosomal recessive disorder and a child who presented with failure to thrive and required transfusions and parenteral nutrition did not improve with LT. In erythropoietic protoporphyria (EPP), there is excessive production of protoporphyrin in the bone marrow. Protoporphyrin is hepatotoxic and pigment loading of hepatocytes and bile canalicular sludging may result in progressive cholestasis and cirrhosis. LT is beneficial for such patients with end-stage liver disease. Perioperative management includes use of filters on operative lights to prevent skin burns and intestinal perforation. Other concerns include development of neuropathy, biliary complications, and recurrent liver disease. This review addresses the rationale, patient selection, evaluation, management issues, and technique of performing LT in various types of porphyria. ***Liver Transpl 13:1219-1227, 2007.***

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The porphyrias are well-defined inherited disorders resulting from deficiency of specific enzymes in the heme biosynthesis pathway and are classified as either hepatic or erythropoietic depending on the primary site of overproduction of the porphyrins or porphyrin precursors. Of the 7 human porphyrias, 5 are hepatic, of which 4 can present with acute attacks, and 2 are erythropoietic (Table 1). Although medical management is the backbone of therapy, we have described a cure after liver transplantation (LT) in a severely affected patient with acute intermittent porphyria (AIP).[1] LT has also been shown to be beneficial in a patient with variegate porphyria (VP), although this was not undertaken for porphyria symptoms.[2] However, LT was not beneficial in a child with severe 5-aminolevulinate dehydratase deficiency porphyria, a very rare autosomal recessive acute porphyria.[3] LT is well established as a treatment for protoporphyrin hepatotoxicity, which occurs in a minority of patients with erythropoietic protoporphyria (EPP).[4,5]

Here, we review the indications, assessment, and posttransplantation management for patients with porphyria with a view to assisting transplant units in developing protocols.

AUTOSOMAL DOMINANT ACUTE PORPHYRIAS

The three autosomal dominant acute hepatic porphyrias, AIP, hereditary coproporphyria, and VP, result from partial enzyme deficiency (Table 1), which affects all tissues and can result in acute attacks that are indistinguishable and for which the standard treatment

Abbreviations: AIP, acute intermittent porphyria; LT, liver transplantation; VP, variegate porphyria; EPP, erythropoietic protoporphyria; HCC, hepatocellular carcinoma.

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TABLE 1. Classification of Porphyrias and the Role of Liver Transplantation

Porphyria type	Deficient enzyme	Inheritance	Neurovisceral symptoms	Photosensitivity	Benefit reported from LT	Principal reference
Hepatic porphyrias						
5-aminolevulinate dehydratase deficiency	5-aminolevulinate dehydratase	AR	+	−	No	3
Acute intermittent porphyria	HMB synthase (PBG deaminase)	AD	+	−	Yes	1
Porphyria cutanea tarda	URO decarboxylase	AD	−	+	Not done	−
Hereditary coproporphyria	COPRO oxidase	AD	+	+	Not done	−
Variegate porphyria	PROTO oxidase	AD	+	+	Yes	2
Erythropoietic porphyrias						
Congenital erythropoietic porphyria	URO synthase	AR	−	+	No rationale	−
Erythropoietic protoporphyria	Ferrochelatase	AD	−	+	Yes	5

Abbreviations: LT, liver transplantation; AR, autosomal recessive; AD, autosomal dominant; XLR, X-linked recessive; ALA, δ-aminolivulenic acid; HMB, hydroxymethylbilane; PBG, porphobilinogen; URO, uroporphyrinogen; COPRO, coproporhyrinogen; PROTO, protoporphyrinogen.

is identical. AIP is the most common acute porphyria, except for in South Africa, where, due to a founder effect VP affects approximately 3 of every 1,000 individuals of Afrikaner descent.[6] Over 200 mutations in the hydroxymethylbilane synthase (porphobilinogen deaminase, uroporphyrinogen-I synthase) gene have been described.[7] Clinical expression is highly variable, with the great majority of those affected never suffering an acute attack. A minority of patients, however, can suffer repeated severe or fulminant attacks with devastating clinical consequences. Hereditary coproporphyria and VP can manifest with bullous cutaneous photosensitivity, which may occur independently or in combination with the acute attack. Other than avoiding sun exposure, there are no effective measures for treating the skin lesions.

Clinical Features and Mechanism of Tissue Damage

In affected individuals, precipitating factors include drugs, fasting, alcohol ingestion, smoking, and stress from illness or surgery. Endogenous hormones, particularly progesterone, play a role and explain why attacks are more common in women.[8]

Neurovisceral symptoms, which are rare before puberty, can be severely disabling and, where the condition has not been diagnosed, may be fatal. Abdominal pain, the most frequent symptom, is usually poorly localized and may be accompanied by vomiting, constipation, distention, and rarely diarrhea. Sympathetic overactivity may result in tachycardia, hypertension, tremors, excessive sweating, urinary retention, cardiac arrhythmias, and sudden death. Acute psychiatric manifestations and seizures may occur, although these are limited to the period of the acute attack. Seizures may be due to hyponatremia, which may be exacerbated by intravenous infusion of sodium-free dextrose. Peripheral neuropathy is due to axonal degeneration, primarily affects motor neurons, and can lead to respiratory and bulbar paralysis and death.

The mechanism for neurological damage is poorly understood and has been attributed to accumulation of porphyrin precursors in neural tissue together with possible neuronal heme deficiency.[9] This hypothesis is supported by the experience following the first LT in an AIP patient.[1] Mild liver function abnormalities have been described in hepatic porphyrias but are usually clinically insignificant.[10] Long-term complications include impaired renal function, chronic systemic arterial hypertension,[11,12] and an increased risk of hepatocellular carcinoma (HCC),[13,14] all of which are more common among patients with severe, recurrent acute porphyria.

Issues With Conventional Treatment and Indications for LT

Most patients require hospitalization during an acute attack for symptomatic treatment, administration of intravenous dextrose, electrolytes, and hemin, and close observation for neurological complications. The standard regimen for hemin therapy is 3 to 4 mg/kg infused once daily for 4 days, although in some patients treatment for longer than 4 days may be considered.[15] When hemin is not immediately available, carbohydrate loading in the form of 10% glucose (300 to 500 gm/24 hours) will also suppress 5-aminolaevulinate synthase, albeit at the risk of aggravating hyponatremia.[16]

Hemin is available as heme arginate in Europe and as lyophilized hydroxyheme (panhematin) in the United States. Intense phlebitis is a major issue, particularly with panhematin, and may compromise venous access

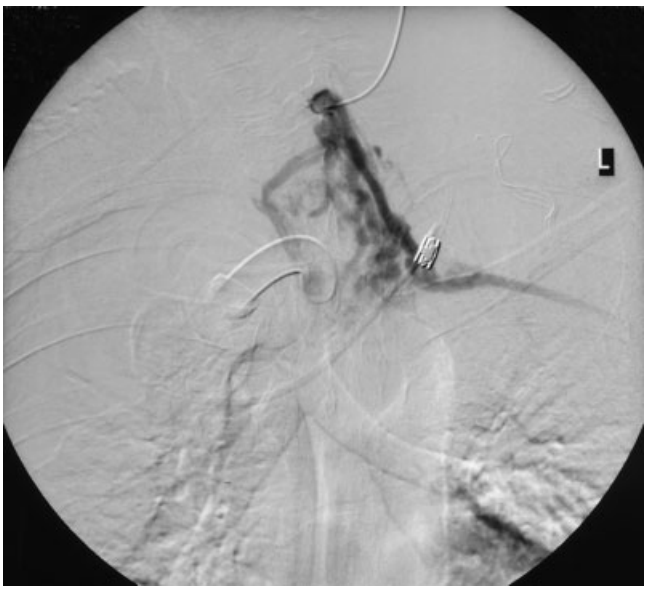

Figure 1. An attempt at venography via a catheter placed in the left internal jugular vein confirms complete occlusion of the left internal jugular vein with formation of multiple collaterals in a 34-yr-old woman with acute intermittent porphyria on weekly heme arginate infusion for several years. Tracheostomy tube is in situ and the clavicle and bronchi are visible in outline.

with repeated administration. Frequent administration, therefore, requires insertion of an indwelling venous catheter (central line) with its associated clinical risks, to allow infusion directly into a large central vein. Reconstitution with albumin enhances the stability of lyophilized hemin and decreases the incidence and severity of phlebitis.[17] We routinely administer heme arginate reconstituted in 20% albumin to reduce the severity of phlebitis as 1 of our female patients with severely disabling acute attacks of AIP could not be offered LT because of lack of venous access following weekly administration of hemin for several years (Fig. 1). Extensive thrombosis of the inferior vena cava below the level of the renal vessels, extending into the iliacs, which formed around a port-a-cath (Portex, Sims Medical, Hythe, Kent, United Kingdom) was recently reported.[18] Not only was AIP precipitated by complications arising from the thrombus but the patient was unable to receive prophylactic hemin. There is a theoretical risk of transmission of Creutzfeldt-Jakob disease or its variant by the use of human albumin but no transmission has been reported in humans. In the Cohn fractionization process being used currently, serial fractions are discarded to diminish the risk of transmission of infections. Since albumin is isolated as the last fraction, there is virtually no chance of transmitting an infection.[19]

We previously reported successful liver transplantation with resolution of AIP in a patient who suffered repeated acute attacks, and who had very poor quality of life.[1] More recently, transplantation has been undertaken at our center in 2 further patients who had experienced life-threatening severe relapsing attacks of AIP requiring prolonged ventilatory support (our unpublished data). In 1 patient the transplant was performed while the patient was still ventilator dependent and she died of septic complications without recovering independence from intensive organ support. A third patient, who was required to recover from many months of artificial ventilation and to be independently mobile prior to transplantation, has made a good recovery. We know of a fourth patient (C. Millson, M.H. Davies, personal communication) who has similarly recovered well from LT with clinical and biochemical resolution of AIP. Based on this experience we recommend that for patients with paralytic attacks, sufficient recovery time be allowed for resumption of spontaneous ventilatory effort; otherwise, the unavoidable requirement for prolonged ventilation following transplantation greatly increase the risks of the procedure in the context of immunosuppression and nosocomial infection. We suggest, as a minimum, waiting until the patient is able to maintain normal blood gases on tracheostomy without pressure support before they are placed on the active LT list. Optimal timing for LT requires careful balancing between the benefits of extended pretransplantation convalescence and the concerns regarding progressive loss of venous access and risk of a neurological relapse from a further acute attack. An acute inflammatory response due to intercurrent infection increases heme precursor production and places the patient at risk of a neurological relapse. In our experience, elevation of C-reactive protein is not a feature of AIP attacks per se but occurs when acute attacks are precipitated by infection. Prioritization for patients awaiting LT is generally according to the Model for End-Stage Liver Disease. Patients with acute porphyria, who have normal liver function, would not meet the necessary criteria and therefore merit special priority on the waiting list for LT. Where possible, regular monitoring of urinary porphobilinogen can be helpful to detect the earliest sign of acute attack and hemin therapy can be commenced. In patients with active AIP, urine porphobilinogen excretion is usually increased between acute attacks, but will increase more than 2-fold over this increased basal excretion rate during an acute attack.[20]

In a single instance we opted to utilize the liver removed from a patient who was transplanted for AIP as donor in a domino transplant. The protocol was approved by the United Kindom's Unrelated Live Transplant Regulatory Authority and fully informed consent was obtained from donor and recipient. The donor's disease was typical of young females in that she had severe cyclical attacks that were ameliorated by gonadotropin release antagonists. Given that AIP typically ameliorates in such patients with aging and that her father who carried the same mutation in the hydroxmethylbilane synthase gene had never suffered an attack of AIP, it was judged ethical to perform a domino transplant to a recipient who was a 65-yr-old man whose HCC had grown to the point at which he was to be withdrawn from our active LT waiting list. Unfortunately, the recipient died of septic complications related to technical surgical problems, which precluded any

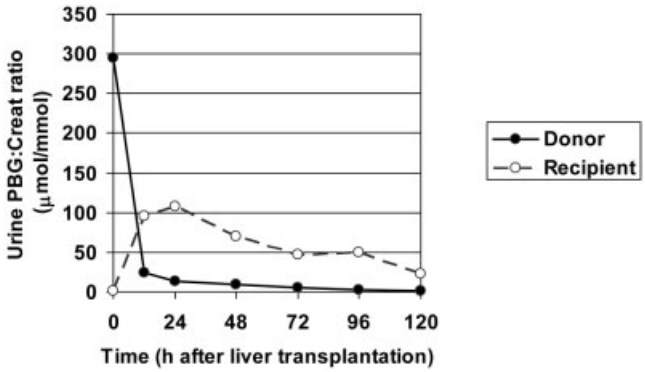

Figure 2. Urinary porphobilinogen (PBG) excretion showing correction of the metabolic defect in the AIP patient following liver replacement but a rise of PBG in the recipient of the domino liver transplant. Results are expressed as a ratio of PBG to creatinine concentration to correct for varying urine concentration (reference range <1.5 μmol PBG per mmol creatinine).

firm conclusions about the wisdom of utilizing such a liver in domino fashion in the future. The recipient had raised levels of porphobilinogen initially but they rapidly reduced (Fig. 2). He developed a neuropathy that may have been an unrelated critical care neuropathy but a porphyric cause could not be excluded.

Evaluation for LT

Several specific factors need to be considered when assessing patients with acute porphyria for LT.

Hematology

Anemia, although not a feature of the disease itself, is relatively common in these severely affected patients, and may result from poor nutrition or renal dysfunction.[11] Iron status should also be evaluated, as repeated infusions of hemin have been noted to result in iron overload (100 mg of hemin contains 8 mg of iron). If transferrin saturation is increased and the serum ferritin is above 1,000 μg/L, treatment to reduce iron should be considered. Hepatic iron overload is reported to reduce long-term survival following orthotopic LT.[21]

Screening for HCC

Retrospective population-based studies in Scandinavia have reported a 60- to 70-fold increase in the incidence and mortality due to HCC in patients with AIP as compared with age- and sex-matched rates.[13] A prospective cohort study of 650 patients with acute porphyria followed for 7 yr in France found 7 cases of HCC vs. an expected national incidence of 0.2.[14] These studies showed that HCC occurred predominantly in the absence of chronic liver disease, and it was suggested that HCC patients without an obvious etiology should be screened for acute porphyria.

Although the mechanism of increased predilection to HCC in acute porphyria is not known, it has recently been postulated that 5-aminolaevulinate can dimerize at supraphysiological concentrations to produce superoxide from a protonated form of 3,6-dihydropyrazine-2,5-dipropanoic acid, which may promote carcinogenesis.[22] Thus, 6-monthly screening with α-fetoprotein and hepatic imaging seems appropriate, particularly for severely affected patients.

Evaluation for Venous Access

Ultrasound or magnetic resonant venography of the great vessels of neck and groin is recommended to assess for venous thrombosis due to prolonged use of central venous catheters and hemin infusions. Access under ultrasound control is advisable. If the femoral vessels are the only ones demonstrated to be patent, it is important to check that the surgeons are not planning to completely cross-clamp the inferior vena cava before relying on this route of access. If this combination is unavoidable, for LT to be performed, surgical access to an upper body great vessel will have to be acquired once the patient has been anesthetized.

Neurological Evaluation

A complete neurological evaluation including imaging and electrophysiological studies should be carried out to demonstrate axonal degeneration and exclude other etiologies of paresis before considering LT.

Evaluation for Osteoporosis

In patients with active acute porphyria, immobility, malnutrition, vitamin D deficiency, and use of low molecular weight heparin and gonadotropin-releasing hormone analogs may contribute to low bone mineral density. Where identified, individual deficiencies should be corrected and low-dose estrogen patches can be considered if necessary to prevent menopausal symptoms due to use of gonadotropin-releasing hormone analogs. Bone densitometry and gynecological evaluation are recommended every 6 months during the treatment, particularly if unopposed estrogens are used.

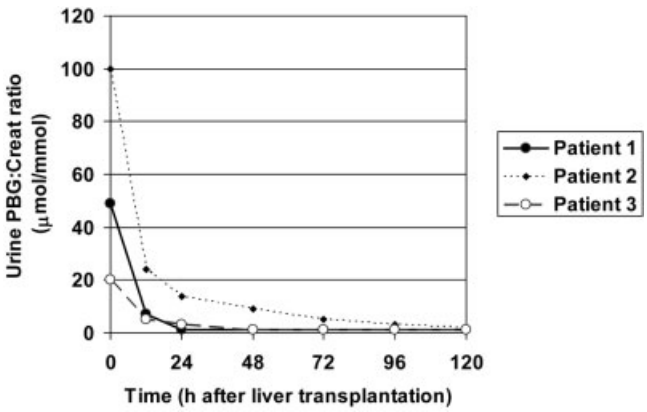

Figure 3. Urinary excretion of heme precursor porphobilinogen (PBG) showing correction of metabolic defect after liver transplantation in 3 patients with acute intermittent porphyria. Results are expressed as a ratio with urine creatinine concentration to correct for varying urine concentration (reference range <1.5 μmol PBG per mmol creatinine).

The use of immunosuppressive agents, in particular corticosteroids, tacrolimus, and cyclosporin A following LT, may lead to further deterioration in bone mineralization, resulting in morbidity and reduced quality of life.[23] In a prospective study, osteopenia was noted in 48.5% and osteoporosis in 23.5% of patients undergoing LT and the use of alendronate along with vitamin D and calcium supplementation prevented bone loss after LT and led to increase in bone marrow density within 24 months.[24] Treatment with bisphosphonates not only prevented deterioration in bone mineral density but also diminished the risk of fractures in postmenopausal women and glucocorticoid-induced osteoporosis.[25,26] The combination of vitamin D3 (400 units or 10 μg daily), calcium (1,000 mg daily), and alendronic acid (5 mg daily) is safe in acute porphyria and should be encouraged, particularly when LT is being considered as a management option. However, in critically ill patients in which alendronic acid may be unsuitable, intravenous or long-acting bisphosphonates should be considered. Deficiency of calcium and vitamin D should be corrected before starting bisphosphonates.

Safety of Drugs Used for LT

Drugs used in patients with acute porphyria may be classified as safe, unsafe, or of uncertain safety with regard to their potential ability to precipitate acute attacks. This information is collated from clinical experience, experimental evidence, usually in tissue culture cells, and knowledge relating to the mechanism of metabolism and excretion. Where a drug is required that is unsafe or of uncertain safety, the risk should be assessed in relation to the potential benefit in the individual patient, taking into account the clinical circumstances at that time. It should also be noted that the transplanted liver, the site of metabolism of most xenobiotics, has normal heme biosynthetic pathway enzyme activity, and the patient should therefore not be at risk of drug-induced acute attacks. However, in view of reports of peripheral neuropathy in patients with acute porphyria in the absence of acute attacks, possibly relating to a heme biosynthesis dysfunction in neuronal tissue, we believe some caution in prescribing should be maintained. At the very least, drugs that have been clearly implicated in causing acute attacks should be avoided in all but life-threatening situations.

The safety of a variety of drugs used during and after LT is summarized in Table 2. The standard immunosuppression protocol for LT at our unit is a combination of corticosteroids, azathioprine, and tacrolimus. Although the safety of tacrolimus is classified as uncertain, it as been used safely in 3 of our patients transplanted for AIP. In addition, a patient with AIP received separate trials of tacrolimus and cyclosporine as part of the pretransplant evaluation for kidney transplantation, without precipitating an acute attack.[27] Management of vancomycin-resistant enterococci may be a problem as the safety of linezolid is uncertain due to lack of data. However, we have used linezolid in our unit without precipitating an acute attack. Teicoplanin, which is not metabolized by the liver, may be an alternative.[28] The use of cotrimoxazole for prophylaxis against pneumocystis carinii pneumonia is contentious as it is known to have induced acute attacks. Dapsone is also unsafe for the same reason. The alternative is to use nebulised pentamidine, which is likely to be safe, but its use is cumbersome. In view of the very low incidence of pneumocystis carinii pneumonia at our center, we prefer not to use any prophylaxis in patients receiving transplantation for porphyria and reserve atovaquone for treatment rather than prophylaxis.

Issues in Anesthesia

Porphyria is always a challenge for the anesthesiologist because of the requirement for administering a number of drugs, sometimes at short notice, to treat unexpected situations.[29] This is particularly true for prolonged and complex operations like LT. Nevertheless, anaesthetic-induced porphyric crises are now extremely rare.[30]

Preoperative assessment should include evaluation for neuropathy, both peripheral and autonomic. Respiratory function should be assessed. Cranial nerve dysfunction may increase the risk of aspiration. Prolonged fasting should be avoided preoperatively and, if necessary, dextrose may be administered intravenously.

Anesthesia is widely understood to be a major risk factor, particularly in previously undiagnosed cases. However, this relates mainly to older induction agents such as thiopentone and methohexitone, which, being barbiturates, are clearly porphyrinogenic. Two alternatives, etomidate and ketamine, are also considered unsafe. These have now been almost entirely superseded by propofol and although animal studies suggest an increased risk, practical experience suggests that it is safe.[31-34] Although propofol may also be used for maintenance, the risk of a crisis also relates to the total dose of drug given, and it may therefore be unwise to use it in this way. Volatile agents are therefore more commonly used. Although data are lacking, our experience suggests that both isoflurane and desflurane are safe (http://www.drugs-porphyria.org). Muscle relaxants like vecoronium and atracurium are safe in our experience.[35] Since patients being considered for LT will have severe neuropathy, it may be possible to manage with little or no neuromuscular blockade. This has the advantage of reducing the total exposure to the drug and reduces the risk of precipitating a crisis. Suxamethonium may be used for rapid sequence induction. Opiates are safe and we have routinely used alfentanil, although data on its safety is lacking. Alternatively morphine is safe and fentanyl, despite being metabolized by cytochrome P450, is widely reported as safe by most drugs advisory services.

To set against these problems, because of the absence of liver disease in acute porphyrias, patients typically have normal coagulation and no portal hypertension. They may therefore be suitable for combined general anesthesia and epidural blockade with procaine or bupivacaine may be used.[36] thus providing the benefit of postoperative analgesia with little respiratory

TABLE 2. Safety of Drugs Commonly Prescribed in Liver Transplant Patients With Acute Porphyria

	Safety		Safety
Immunosuppressants		Analgesics	
Azathioprine	Uncertain[N]	Paracetamol	Safe[UK,N]
Cyclosporin	Safe[UK]	Codeine	Safe[UK,N]
Daclizumab	Safe[N]	Morphine	Safe[UK,N]
Hydrocortisone	Safe[UK]	Tramadol	Unsafe[UK,N]
Methyl prednisolone	Safe[UK]	Alfentanil	Safe[UK,N]
Mycophenolate	Uncertain[N]	Diuretics	
Prednisolone	Safe[UK]	Furosemide	Safe[UK,N]
Sirolimus	Uncertain[N]	Spirinolactone	Unsafe[UK,N]
Tacrolimus	Uncertain[N]	Amiloride	Safe[UK,N]
Antimicrobials/antivirals/antifungals		Antiemetics	
Acyclovir	Safe[UK,N]	Cyclizine	Unsafe[N]
Amphoterecin	Safe[UK]	Domperidone	Safe[UK]
Atovaquone	Safe[UK,N]	Metoclopramide	Uncertain[N]
Ciprofloxacin	Safe[UK]	Ondansetron	Safe[UK,N]
Co-amoxyclav	Safe[UK]	Granisetron	Safe[N]
Co-trimoxazole	Unsafe[UK,N]	Miscellaneous	
Dapsone	Unsafe[UK]	Aspirin	Safe[UK,N]
Fluconazole	Unsafe[UK,N]	Enoxaparin	Safe[UK]
Ganciclovir	Safe[UK,N]	Soluble insulin	Safe[UK,N]
Imipenem + cilastatin	Uncertain[N]	Sodium bicarbonate	Safe[UK,N]
Linezolid	Uncertain[N]	Magnesium sulfate	Safe[UK,N]
Meropenem	Uncertain[N]	Senna	Safe[UK,N]
Pentamidine	Safe[UK]	Ursodeoxycholic acid	Safe[N]
Piperacillin + tazobactam	Uncertain[N]	Noradrenaline	Safe[UK]
Valganciclovir	Safe[N]	Pravastatin	Uncertain[N]
Vancomycin	Safe[UK,N]	Rosuvastatin	Safe[UK,N]
Acid suppressants		Hepatitis A vaccine	Safe[UK,N]
Ranitidine	Safe[N]	Hepatitis B vaccine	Safe[UK,N]
Omeprazole	Safe[UK]	Hepatitis B immunoglobulin	Safe[UK,N]
Lansoprazole	Uncertain[N]	Bisphosphonates	Safe[UK,N]
Pantoprazole	Uncertain[N]	Thiamine	Safe[UK,N]
Esomeprazole	Uncertain[N]	Fluoxetine	Safe[UK,N]
Sucralfate	Safe[UK,N]	Chlorpromazine	Safe[UK,N]
Antihypertensives		Haloperidol	Safe[UK,N]
Ramipril	Uncertain[N]	Acetylcysteine	Safe[UK,N]
Perindopril	No data, avoid	Vitamin D	Safe[UK,N]
Amlodipine	Uncertain[N]	Calcium	Safe[UK,N]
Atenolol	Safe[UK,N]		

NOTE: Drugs are classified as safe, unsafe, or uncertain based on information available from a safe drugs list developed in Cardiff and the Nordic drug database (http://www.drugs-porphyria.org). The clinical risk vs. benefit should be assessed before using a drug classified as uncertain, where necessary with assistance from a specialist porphyria center (see http://www.porphyria-europe.org).
Abbreviations: N, data from Nordic drug database; UK, data from Cardiff safe drug list.

depression. The risks and consequences of epidural blockade should be fully discussed with the patient beforehand so that temporary postoperative weakness caused by the epidural is not assumed to be due to an exacerbation of the neuropathy.

Long-Term Follow-Up After LT for Acute Porphyria

In all 3 of our patients who underwent LT for AIP, the levels of urinary heme precursors rapidly returned to normal after LT (Fig. 3). One of our patients has remained entirely free from acute attacks of porphyria over 4 yr of follow-up and has given birth to a healthy child. Her nerve conduction studies remain normal as does her urinary porphobilinogen excretion. As illustrated by the successful pregnancy described above, genetic counseling for additional family members should not be forgotten.

ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

EPP results from diminished activity of ferrochelatase, the final enzyme in the heme biosynthetic pathway.[37] Enzyme activity is reduced to 10 to 35% of normal in all tissues by a molecular mechanism that is now understood.[38] although the excess protoporphyrin is produced mainly from the bone marrow.[39] The resulting

accumulation of free protoporphyrin, primarily in skin, results in acute painful photosensitivity that usually manifests during early childhood. There may be few obvious clinical signs and diagnosis is frequently delayed.[40] Treatment relies on sunlight avoidance, and patients report a marked reduction in quality of life.

A small minority of EPP patients develop chronic liver disease due to pigment-loading of hepatocytes and bile canalicular sludging. Inadequate biliary excretion of protoporphyrin has a toxic effect on hepatobiliary structure and function.[41] Hepatocyte cytoplasmic protoporphyrin has been demonstrated by microfluorospectrophotometry and polarized light microscopy.[42,43] It has been demonstrated that protoporphyrins impair bile formation and alter the activity of hepatic membrane bound enzymes.[44,45] Bile formed has been shown to be toxic and leads to damage to the bile duct epithelium, resulting in biliary fibrosis.[46] In patients with progressively worsening liver dysfunction, attempts have been made to slow down the deterioration. These include measures to suppress erythropoiesis such as hypertransfusion and/or hemin infusion and measures to increase excretion by plasmapheresis, administration of activated charcoal or bile acid sequestrants.[47-49] The safety and efficacy of ursodeoxycholic acid in enhancing biliary excretion of protoporphyrin remains to be established.

There are several reports of successful LT for patients with EPP and cirrhosis of liver with liver failure.[50-54] At our center, we have performed LT for 2 patients with EPP. One of them, transplanted at the age of 40 yr, has normal liver function and histology at 19 yr of follow-up.[55]

Perioperative Considerations

Perioperative management should include measures to reduce protoporphyrin levels in order to reduce the risk of acute neuropathy and protoporphyrin-mediated damage to the transplanted liver. This may be achieved through the use of exchange transfusion, hemin infusion, or plasmapheresis.[56,57] Neuropathy causing abdominal and limb pain may be present and also helped by these procedures prior to transplantation. During surgery, operative lights cause harm by producing photocutaneous and photovisceral damage. Third degree skin burns adjacent to the surgical incision and multiple small bowel perforations have been reported.[55] The use of special filters (CLS-200-X; Madico Inc., Woburn, MA), is recommended to filter wavelengths that excite protoporphyrin (400-410 nm). These clear filters cause minimum distortion of vision and do not impede surgery. However, first and second degree skin burns may occur despite the use of these filters, which were principally designed to block transmission of ultraviolet-A and ultraviolet-B light.

Patient Survival, Graft Survival, and Complications

The long-term patient and graft survival rates, recurrence of EPP liver disease, and management issues in 20 patients who underwent LT in the United States between 1979 and 2004 were recently reported.[5] The explants were black in color and showed active hepatocellular necrosis, portal inflammation, cholestasis, and extensive deposits of dark brown pigment in hepatocytes, biliary structures, and Kupffer cells. Choledochoduodenostomy was the most common biliary reconstruction used. Postoperative neuropathy manifesting as severe motor weakness requiring prolonged ventilation for up to 7 weeks occurred in 6 of the 20 patients. Biliary complications were seen in 9 out of 20 patients (anastomotic strictures in 5, biliary calculi in 2, anastomotic biliary leak in 1. and displacement of the t-tube in 1) and cytomegalovirus disease in 8 patients. Recurrent EPP liver disease occurred in 11 (65%) of the 17 patients who survived more than 2 months after LT. Recurrent EPP liver disease was noted as early as 8 months after LT and 3 patients were retransplanted at 1.8, 12.6, and 14.5 yr. A total of 3 additional patients who died with recurrent EPP liver disease had extensive protoporphyrin deposits and bridging fibrosis or cirrhosis on liver biopsy. The overall patient and graft survival rates after LT were 85% at 1 yr, 69% at 5 yr, and 47% at 10 yr. In view of the continued production of protoporphyrin by the bone marrow after LT, hematin infusion and/or plasmapheresis have been used to decrease photosensitivity and diminish the risk of recurrent EPP disease and to treat recurrent allograft dysfunction.[58] However, long-term administration of hematin carries additional clinical risks, as described in the section on acute porphyrias. Bone marrow transplantation has been shown to correct the ferrochelatase activity and, thus, the excess production of protoporphyrin.[59] Thus, where possible, bone marrow transplantation may be used to prevent or stabilize recurrent EPP liver disease, as has recently been shown.[60] EPP, therefore, is the most established indication for LT for porphyria but the treatment is not directed at the cause of the disease. The use of hemin and plasmapheresis prior to LT decreases the bilirubin level, thus lowering the Model for End-Stage Liver Disease score. These patients, therefore, also merit special consideration when being listed for LT during EPP crisis.

CONCLUSION

LT has been successful in achieving apparent cure in patients with AIP and may therefore be considered as a valid treatment option for selected patients with recurrent attacks and significant, disabling neurological dysfunction. However, the high risk of carrying out LT must be weighed against the potential benefit in someone with poor quality of life, and the timing of LT is crucial. In chronically affected patients developing vascular thrombosis because of repeated hemin administration, the procedure should be undertaken when at least 2 out of 6 major veins used in clinical practice, including 1 internal jugular vein for measurement of central venous pressure, are still patent. LT should ideally be delayed until a significant degree of neurological recovery has occurred, to facilitate early discharge

from intensive care units. Our experience indicates that performing transplantation on patients who are undergoing intensive care for paralytic episodes is inadvisable as treatment is preventative and will not restore neuronal dysfunction that has already occurred. LT has been successfully performed for VP but cannot be currently recommended for 5-aminolaevulinate dehydratase deficiency porphyria. LT is recommended for EPP when complicated by liver failure. If a matched sibling is available, early bone marrow transplantation is likely to prevent or stabilize recurrent EPP liver disease.

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