LIVER DISEASE IN ERYTHROPOIETIC PROTOPORPHYRIA: INSIGHTS AND IMPLICATIONS FOR MANAGEMENT

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The porphyrias are a group of disorders caused by defects in haem biosynthesis (fig 1). Of the seven main types of porphyria recognised, two are characterised by associated liver disease (table 1). In porphyria cutanea tarda it is the liver disease which leads to the onset of the porphyria, characterised by blistering, hirsutes and skin fragility of sun-exposed skin. A number of different liver diseases may precipitate porphyria cutanea tarda including haemochromatosis, alcoholic liver disease and hepatitis C. In contrast, in erythropoietic protoporphyria (EPP) it is the porphyria itself which leads to liver disease, due to progressive deposition and accumulation of insoluble protoporphyrin IX in hepatocytes and bile canaliculi.

EPP is an inborn error of haem biosynthesis caused by mutations in the gene encoding the mitochondrial enzyme ferrochelatase (FECH), the final enzyme in the haem biosynthetic pathway (fig 1).[1–5] It was first described by Magnus *et al* in 1962.[6] Ferrochelatase catalyses the insertion of ferrous iron into protoporphyrin to form haem, and when defective or deficient, accumulation of protoporphyrin ensues. Ferrochelatase is active in cells that produce haem including erythroid precursors in the bone marrow[7] and hepatocytes.[8] However, the majority of protoporphyrin (80% or more) originates from bone marrow with most of the remainder generated by the liver (fig 2).[7 9]

Protoporphyrin accumulates in the maturing red blood cells during haematopoiesis. When red cells enter the circulation, free protoporphyrin diffuses across the red cell membrane and binds to plasma proteins. The liver extracts protoporphyrin from the plasma, most of which is excreted unchanged into the bile, with the remainder metabolised (by liver ferrochelatase) to haem. Some protoporphyrin is subsequently reabsorbed in an enterohepatic circulation.[10]

Protoporphyrin-induced hepatotoxicity is a rare complication occurring in 1–5% of patients, for whom liver transplantation is often required. Since the first liver transplant for EPP in 1980,[11] more than 40 further liver transplants have been carried out as treatment for advanced liver disease in this condition. However, liver transplantation fails to correct the underlying metabolic deficiency and protoporphyrin damage to the transplanted liver is likely.

EPP is an inherited disorder with both recessive[12–16] and dominant patterns of inheritance (fig 3A, B). In most patients with EPP, disease-causing mutations are present on one allele in association with co-inheritance of a low-expression allele.[17] This has been demonstrated by case-control association in 39 families with EPP.[18] Using haplotype segregation analysis, a polymorphism was identified in intron 3 (IVS3-48C) that increases the use of an aberrant splice site.[19] The aberrantly spliced mRNA has been shown to be subject to more rapid degradation resulting in a decreased steady-state level of mRNA, leading to a further reduction in FECH enzyme activity and disease expression.[19] The low-expression variant IVS3-48C has a prevalence in the white population of France of about 10%.[18] Co-inheritance of a *FECH* mutation and the low-expression allele accounts for nearly all cases of expressed EPP,[20–23] with estimated true autosomal recessive inheritance accounting for about 3% of cases.[23] Very rarely, alternative mechanisms may reduce FECH activity below the critical threshold for symptomatic disease, including deletion of an *FECH* gene secondary to leukaemia[24] or a dominant negative effect from the mutant *FECH* allele.[25]

The *FECH* gene was cloned and sequenced in 1990[26] and subsequently localised to the long arm of chromosome 18 (18q22.31).[27] It spans 45 kb and contains 11 exons which code for an enzyme with 423 amino acid residues.[28] The enzyme functions as a dimer, which may have reduced stability and catalytic activity in the presence of a mutated subunit.[29] Allelic heterogeneity of the molecular defects in the *FECH* gene has been demonstrated.[30] Analysis of the genetic mutations in EPP reveals three main categories:

- Nucleotide substitutions: missense and nonsense mutations caused by single nucleotide substitutions in the coding region; nonsense mutations are null.
- Splice site mutations: these may produce truncated proteins but this has never been directly shown for EPP. Furthermore, these mutations do not always produce stable mRNA transcripts; they may be null or may preserve some activity.

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- Frameshift mutations resulting in premature stop codons are always null, the mechanism being accelerated RNA decay.

Minder *et al* described a significant genotype-phenotype correlation between so-called "null allele" mutations and protoporphyrin-related liver disease in EPP.[31] This supported an earlier report which showed major structural alteration in the FECH protein in all of eight cases undergoing liver transplantation for EPP-associated liver failure.[32 33] However, as more data accumulate, it is increasingly clear that the *FECH* gene mutations by themselves do not account for the severe liver disease phenotype, as the same mutations have now been reported both in asymptomatic family members and in patients from families in which liver disease had not occurred.[33 34] There is currently no way reliably to identify patients at risk, and no intervention that is uniformly effective in restoring normal liver function once hepatic failure ensues.

LIVER DISEASE IN EPP

No study to date has specifically set out to document the natural history of liver disease or to identify risk factors in its causation in a large unselected cohort of unrelated patients with EPP. The largest studies reported so far have all been from single centres and many are subject to case selection bias resulting from local interest and expertise in the management of EPP-related liver disease. Despite these shortcomings, these studies (summarised in table 2) provide a useful starting point for further analysis of this topic.

PATHOGENESIS OF LIVER DISEASE IN EPP

Irrespective of its origin, excess protoporphyrin is excreted by the liver into bile and enters an enterohepatic circulation. Protoporphyrin is a hydrophobic compound which is not filtered by the kidneys. When in excess, protoporphyrin becomes insoluble in bile and exerts cholestatic effects leading to architectural changes in the hepatobiliary system ranging from mild inflammation to fibrosis and cirrhosis.[42] Even in early EPP, ultrastructural damage has been described in hepatocyte nuclei, endoplasmic reticulum, plasma membranes and bile canaliculi, associated with protoporphyrin crystals.[43] Significant intracellular precipitates of protoporphyrin, demonstrated in liver biopsy samples by fluorescent birefringence, are invariably present in protoporphyric liver disease.[44]

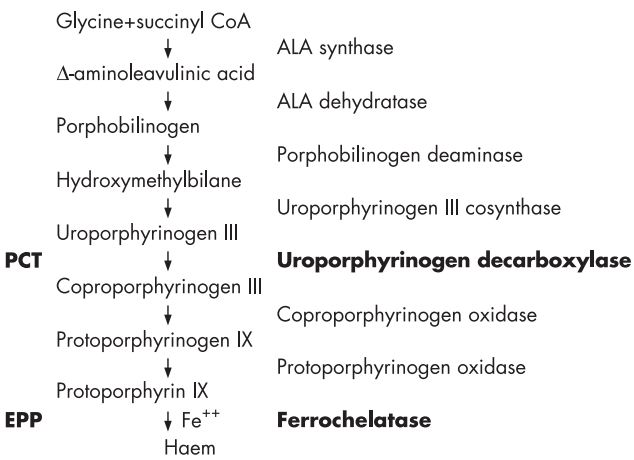


Figure 1 The haem biosynthetic pathway showing the enzyme deficiency associated with porphyria cutanea tarda (PCT) and erythropoietic protoporphyria (EPP). The final step in this pathway involves the incorporation of iron into the middle of the ring structure of protoporphyrin IX to form haem.

Exposure of cultured hepatocytes to protoporphyrin inhibits cell metabolism and increases cellular fragility.[45] However, it remains unclear what effect protoporphyrin has on hepatocytes in vivo and how this relates to the development of liver disease. Bloomer *et al*[32] found that liver FECH activity in EPP-related end-stage liver disease was reduced more than could be explained by the decrease in ferrochelatase protein, and concluded that the liver probably contributes to the over-production of protoporphyrin that results in its own damage. In the absence of a clear explanation for occasional severe liver disease complicating EPP in humans, Nordmann[46] speculated that patients may vary in their susceptibility to protoporphyrin-induced liver damage. This is probably so, but host factors other than deficiency of FECH activity relevant to the onset and progression of liver disease are currently unknown. Recent murine studies (highlighted later in this review) have revealed that other genetic factors are relevant to this process. It is likely that quantitative trait loci analyses will shed more light on this important topic, with the growing recognition of the importance of such factors for many inherited diseases.

Hepatobiliary disease in humans with EPP may be described under the following headings:

- Cholelithiasis;
- Mild liver disease;
- Deteriorating liver disease; and
- Terminal phase of EPP-associated liver disease.

Cholelithiasis

Protoporphyrin in bile may crystallise out forming stones. The original case of EPP described by Magnus in 1961 underwent a cholecystectomy at the age of 29 years and a solitary gallstone was identified.[6] Gallstones have subsequently been reported in EPP in many patients, including 2 patients in a series of 29 from Denmark,[35] 4 patients in a series of 32 reported from the USA,[36] and 9 patients from a series of 200 reported from The Netherlands.[37] Three of the patients in the series from the USA required cholecystectomy, and gallstones analysed from 2 of these cases revealed high levels of protoporphyrin.[36] Todd highlighted the fact that, when gallstones occur in children, EPP should be included in the differential diagnosis.[47]

Mild liver disease

There is wide variation in the severity of liver disease in EPP. Minor abnormalities in biochemical parameters of liver function are relatively common and include raised aspartate transaminase levels and approximately twofold increases in alkaline phosphatase and γ-glutamyl transferase.[44] A study of 32 patients with EPP included a single patient with abnormal liver function.[36] Analysis of liver biopsies from this case and 4 patients with normal liver function revealed protoporphyrin deposition without evidence of fibrosis or infiltrates in all 5 samples.[36] In contrast, liver biopsies from 7 cases of EPP without overt liver disease from The Netherlands showed protoporphyrin deposition and mild fibrosis in 3 cases; the remainder were normal.[48] In a separate study Cripps *et al* also reported protoporphyrin deposition in liver biopsy specimens

Table 1 Liver disease and the porphyrias: names and patterns of inheritance for the seven main clinical variants of porphyria, highlighting those characterised by concomitant liver disease

Disorder	Liver disease	Inheritance
ALA dehydratase porphyria	No	Autosomal recessive
Acute intermittent porphyria	No	Autosomal dominant
Congenital erythropoietic porphyria	No	Autosomal recessive
Porphyria cutanea tarda	Yes	Complex
Hereditary coproporphyria	No	Autosomal dominant
Variegate porphyria	No	Autosomal dominant, incomplete penetrance
Erythropoietic protoporphyria	Yes	Autosomal recessive (very rare) and autosomal dominant incomplete penetrance

from 5 patients with EPP and normal liver function tests; portal and periportal fibrosis was identified in 2 of these 5 samples.[49] An ultrastructural study of liver biopsy specimens obtained from 11 patients with EPP, 4 of whom had overt liver disease and 7 of whom did not, revealed significant pathological changes in all samples compared with normal controls.[50] It was concluded that liver damage is an early and consistent feature of EPP.[50] Finally, a study with histopathology and ultrastructural studies of liver biopsy samples obtained from 4 patients with EPP (1 with severe liver disease, 1 with mild liver disease and 2 without evidence of liver disease and with normal histopathology) showed characteristic crystal-containing vacuoles on electron microscopy in all 4 cases.[51] It therefore appears that protoporphyrin deposition in hepatocytes is invariable, whereas histological evidence of damage is less common; electron microscopy will, however, show ultrastructural evidence of damage in most, if not all, patients with EPP.

Deteriorating liver disease

Patients with EPP who manifest significant liver disease will progress to decompensated cirrhosis which, in the absence of liver transplantation, is fatal. Various treatments have been attempted to preserve liver function and break the cycle of rapid deterioration that occurs in this situation in order to avoid terminal liver failure, or at least to buy time until a donor liver becomes available. The different forms of treatment have been directed at specific pathogenetic mechanisms as follows:

- To increase the excretion of protoporphyrin into bile by the oral administration of the bile salts chenodeoxycholic acid[50 52] or ursodeoxycholic acid.[41]
- To reduce protoporphyrin production by suppressing erythropoiesis using iron,[53 54] red cell transfusions[55] or infusion of haematin,[56 65] all of which are intended to reduce the drive for haem synthesis.
- To reduce the pool of circulating plasma protoporphyrin by plasmapheresis,[57 58] haemodialysis,[59] and exchange transfusions.[55 60]
- To reduce protoporphyrin levels by interrupting the enterohepatic circulation with administration of cholestyramine[59 61] and activated charcoal.[54 62]
- To reverse oxidative stress in EPP by intravenous vitamin E therapy.[63]

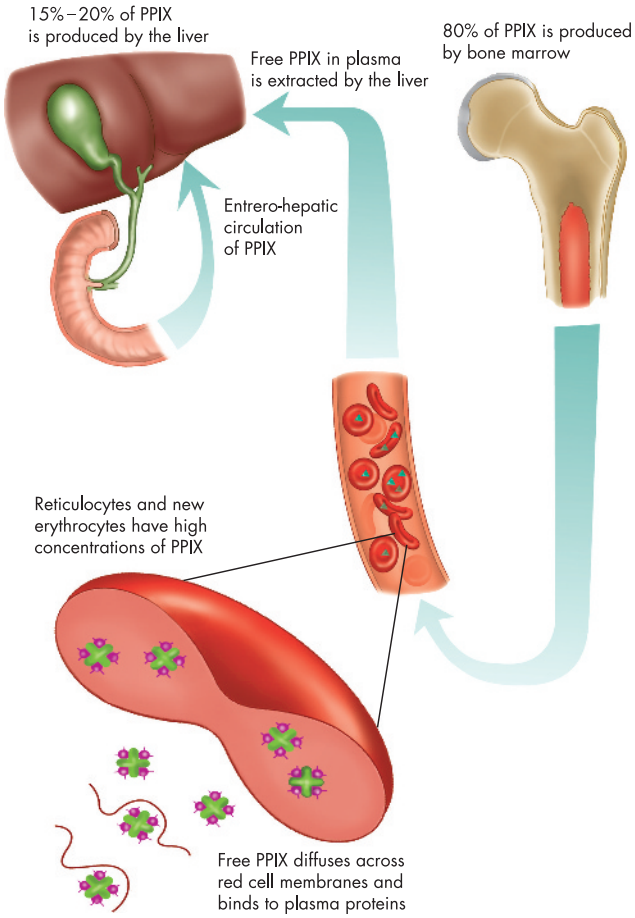


Figure 2 The fate of protoporphyrin IX in erythropoietic protoporphyria.

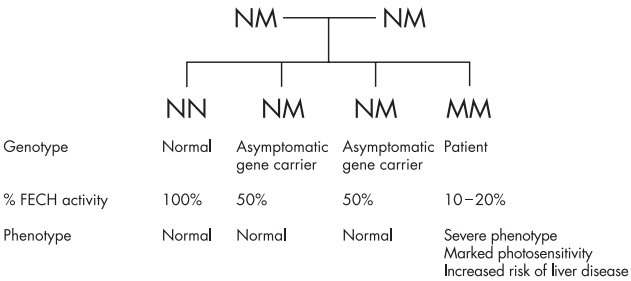
One or more of these treatments are sometimes combined,[58 59] and this is currently the practice before liver transplantation in order to optimise the environment into which the new liver is transplanted.[64 65] However, none of these treatments is effective in all cases, each has potential problems and none has been applied in sufficient numbers of patients to allow a rigorous evaluation of efficiency.

Treatment with bile acid appears to have only a modest effect on EPP-associated liver disease. Administration of chenodeoxycholic acid resulted in no distinct improvement in ultrastructural assessment of organelle damage in EPP-associated liver disease in three patients after 1 year of treatment,[50] and its therapeutic efficacy in another study was doubtful.[52] In spite of these reports, chenodeoxycholic acid continues to be used with other treatments for the treatment of acute liver decompensation before transplant surgery.[64] Doss and Frank reported a patient who showed biochemical and clinical improvement from EPP-induced decompensated liver cirrhosis following treatment with cholic acid.[66]

The role of iron treatment in EPP is unclear, with reports of significant efficacy[53 54] but also reports of increased protoporphyrin levels in some patients.[67 68] Furthermore, use of erythropoietin following orthotic liver transplantation in one patient was implicated in causing a great overproduction in protoporphyrin IX, prompting the authors to conclude that

A

Autosomal recessive pedigree; accounts for 3% of cases of EPP



B

Pedigree resembling an autosomal dominant disease with incomplete penetrance; accounts for 97% of cases of EPP

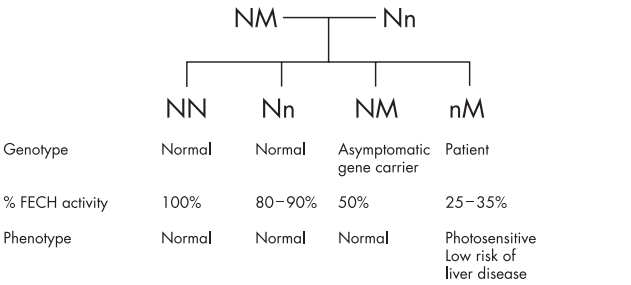


Figure 3 Genetics of erythropoietic protoporphyria (EPP) and relationship between genotype and ferrochelatase activity (expressed as a percentage of normal). (A) Autosomal recessive inheritance. (B) Autosomal dominant inheritance due to co-inheritance of low-expression and mutant alleles. FECH, ferrochelatase; N, normal ferrochelatase gene; M, mutant allele; n, low-expression allele.

treatment with erythropoietin is risky and probably contra-indicated in EPP.[69] Transfusion therapy is probably the most widely reported and effective treatment for deteriorating liver function in EPP,[55 70–74] but in one case it was implicated as the trigger for worsening liver function.[75] Various hypertransfusion protocols for decompensating EPP have been used, ranging from 1 unit of blood per month for 5 months to a maximum of 1 unit every 2–7 days repeated 3–10 times.[55 70–74] However, care is needed as transfused cells exposed to plasma protoporphyrin are more fragile than endogenous protoporphyrin-loaded erythrocytes.[75 76 77] The risk of haemolysis can be reduced by plasmapheresis conducted before transfusion and, in the context of liver transplantation, immediately before surgery.[65] Exchange transfusion is seldom used and is reserved for severe or rapidly deteriorating cases. Intravenous haematin has been shown to reduce protoporphyrin levels[56 66 78 79] and, more recently, haem-albumin has been used successfully in combination with plasmapheresis before liver transplantation.[65] Haemodialysis has only been used as a treatment in EPP-related liver failure and was unsuccessful.[59]

The efficacy of oral cholestyramine was reported in two well documented cases.[80 81] The therapeutic use of this agent in EPP-related liver disease is seldom reported and, when used, it is usually in combination with other treatments.[59 64] Some patients, however, fail to respond to this treatment.[66] Cholestyramine was the main treatment used in a 36-year-old patient with EPP who developed liver disease but remained in good health until rapid deterioration in liver function 6 years

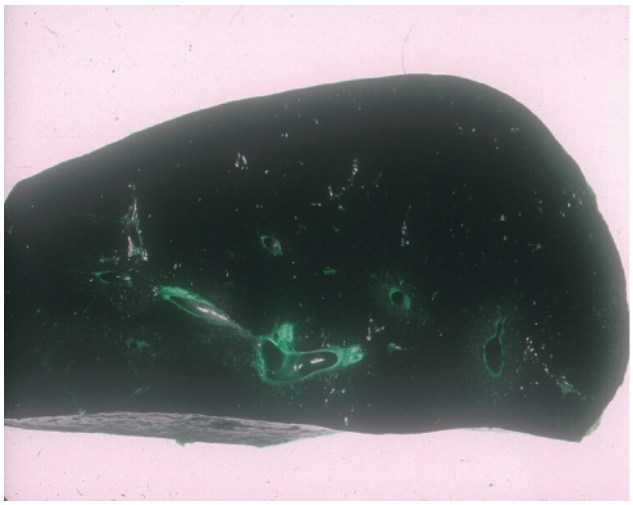


Figure 4 Liver disease in erythropoietic protoporphyria. An explanted liver showing black colour due to diffuse deposition of protoporphyrin pigment.

Table 2 Patient series with erythropoietic protoporphyria (EPP) worldwide with details of liver disease

First author	Year	Country	No of patients	% with hepatobiliary disease	Comment
Schmidt[35]	1974	Denmark	29	3%	Biochemistry not performed in all cases; 1 patient with porphyrin deposits in liver biopsy
DeLeo[36]	1976	USA	32	4%	No severe liver disease
Went,[16] Baart de la Faille[37]	1984	Netherlands	200	6%	9 with gallstones, 3 young patients with cirrhosis
Murphy[38]	1985	UK	382	>1%	3 patients with acute hepatic failure
Gross,[41] Lehmann,[40] Frank[39]	1998	Germany	140	~25%	Severe liver disease in 10% of patients
Minder,[31] Rüfenacht[30]	2002	Switzerland and France	55	16%	9 patients with liver disease
Chen[33]	2002	USA	34	41%	Highly selected series. Included 10 patients who underwent liver transplant
Wiman[20]	2003	Sweden	9	10%	1 patient with severe liver disease requiring liver transplantation

later requiring liver transplantation.[82] Activated charcoal is another treatment aimed at preventing reabsorption of protoporphyrin from the gut, and has the merit of being cheap and safe, albeit unpalatable.[54 62] Long-term treatment (27 months) with this agent has been reported to be beneficial in reducing protoporphyrin levels and restoring liver function.[62] Finally, intravenous vitamin E was reported to be effective at reversing severe EPP-related liver disease in a single case report.[63]

Terminal phase of EPP-associated liver disease

Deteriorating liver disease in EPP is characterised by cholestasis[83] followed by jaundice and generalised upper abdominal pain.[66] The spleen becomes enlarged and haemolysis may ensue.[75] Rapidly worsening photosensitivity due to a further reduction in biliary free protoporphyrin excretion heralds the onset of fulminant disease which is seldom reversible and, in the absence of liver transplantation, usually leads to death. Acute liver failure may rarely be the presenting feature for EPP.[85] Additionally, EPP-related liver failure may sometimes be further complicated by the development of acute pancreatitis.[86] In 1986 Bonkovsky and Schned[87] summarised 21 fatal cases of EPP-related liver failure reported in the literature, and Todd identified a further 8 cases in his comprehensive review in 1994.[3] The majority of these fatal cases were over the age of 30, but two teenagers and an 11-year-old child were also included.[3] In the last 10 years liver transplantation has increasingly been available as a treatment option but, despite this, patients have continued to die from EPP-related liver failure.[30 59 88]

The cycle of deterioration which characterises fulminant hepatic failure in EPP has been recorded in detail in a number of individual case reports, but the initiating event (or events) remains unclear. What is known is that cholestasis induced by protoporphyrin leads to further accumulation of protoporphyrin,[45] initiating a vicious cycle of worsening cholestasis and reduced protoporphyrin excretion.[45] Haemolysis leads to increased erythropoiesis, hence increased de novo porphyrin formation by the bone marrow.[75] Once this cycle is established, liver decompensation is rapid and liver failure ensues (figs 4 and 5).

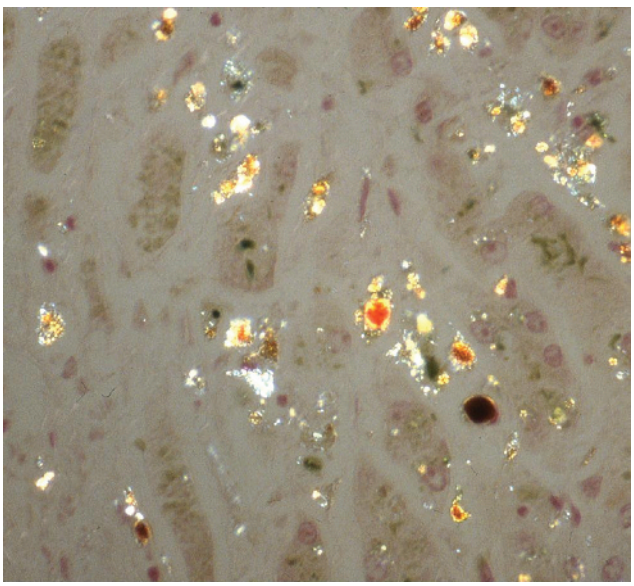


Figure 5 Magnification ×20 of liver histology from fig 4 showing the birefringence of pigment deposits due to the presence of protoporphyrin crystals.

LIVER TRANSPLANTATION IN EPP

The first liver transplant for EPP-related liver disease was carried out in 1980.[11] Since then, more than 40 further liver transplants have been reported (table 3). Published reports with clinical details of liver transplantation for EPP-related liver disease include 41 patients (23 male) of age range 13–59 years (mean 39.2 years). The most recent figures from the European Liver Transplant Registry indicate that 19 liver transplants were performed in Europe for EPP between 1985 and 2003, 13 of whom have survived. The reasons for the deaths were gastrointestinal haemorrhage (n = 1), primary graft non-function (n = 1), infection (n = 2) and unknown causes (n = 2) (V Karam, personal communication, July 2005).

McGuire *et al*[84] have recently reported the outcome of 20 cases of EPP in the USA who underwent liver transplantation. Paediatric and adult survival rates were 100% and 85% respectively at 1 year, 75% and 69% at 5 years and 50% and 47% at 10 years. Recurrent EPP was noted in 11 of the 17 patients (65%) who survived more than 2 months after transplantation. Of the remaining 6 patients without evidence of recurrent EPP, serial monitoring of liver function has shown no evidence of cholestasis. The earliest interval at which recurrent disease was noted on liver biopsy was 8 months. Three patients were re-transplanted for recurrent EPP-associated liver disease at 1.8, 12.6 and 14.5 years. Three additional patients in this series died 61–73 months after liver transplantation, documented by extensive protoporphyrin deposits and bridging fibrosis or cirrhosis on liver biopsy. The high rate of recurrent EPP-associated liver disease prompted the authors to recommend that bone marrow transplantation (soon after successful liver transplantation) should be considered in transplant recipients in order to correct the underlying defect and prevent this.

Liver transplantation restores normal liver function and thus the ability to excrete protoporphyrin via the biliary system. However, it does not correct the FECH enzyme deficiency in the bone marrow, which continues to be the source of significant overproduction of protoporphyrin. Transplanted patients therefore usually continue to have the symptoms of EPP and are at risk of developing EPP-related liver disease in the transplanted liver;[41 89 90 104] some patients have subsequently required a second transplant.[84]

A number of early patients with EPP who received a liver transplant developed life-threatening phototoxic abdominal burns and wound dehiscence with severe haemolytic anaemia, since it had not been foreseen that prolonged visceral exposure to operating lamps would result in tissue phototoxicity analogous to that displayed in the skin under normal circumstances.[82 106] Additional and unexpected complications included acute neuropathy[82 101 106] resulting from high circulating protoporphyrin levels (neuropathy is not generally a feature of EPP as it is of other forms of porphyria), and acute protoporphyrin-mediated damage to the transplanted liver resulting in delayed return of function as a result of these high circulating levels at the time of grafting.[41 89 90] This led to

Table 3 Published clinical reports of liver transplants for erythropoietic protoporphyria (EPP)-related liver failure

First author	Year	Sex	Age	Complications	Outcome
Wells[11]	1980	M	19	Death at 4 weeks after transplantation	Death attributed to disseminated candidiasis
Polson[91]	1988	M	13	Initially none	First liver rejected. Death from complications after second liver transplant
Samuel[9]	1988	F	24	Transplanted liver functioned poorly initially	Alive at 40 months. Good outcome
Bloomer[92]	1989	F	38	None	Patient well 13 months after transplant but with mild hepatic fibrosis in transplant
		M	51	Severe skin necrosis and photo-injury to intestines	Death secondary to multiple intestinal perforations
Wagner[93]	1989	M	49	Sepsis	Died 2 months after transplant
Herbert[82]	1991	F	42	Skin burns and neuropathy	Slow recovery. Alive at 36 months
Shehade[95]	1991	F	40	Skin burns and severe neuropathy	Well 3 years after transplant. Mild neuropathy persisted
Steinmüller[94]	1992	M	51	Successful transplant	Well 1 year after transplant
Mion[64]	1992	M	38	Postoperative seizures	Medium term survival (at least)
Ozawa[96]	1992	M	15	Surgery successful	No follow-up published
Schleiffenbaum[97]	1992	F	40	Surgery successful	Patient well 5 months after transplant
Key[75] (Bloomer[32])	1992	M	51	Skin burns, small GI bleed, severe haemolytic anaemia	Sepsis and death 73 days after surgery
	1992	M	13	Severe motor neuropathy, severe haemolytic anaemia	Good recovery following surgery
Sarkany[13]	1993	F	17	None	Well 14 months after surgery
Rank[98]	1993	F	36	Postoperative bleeding	Multiorgan failure; death 5 weeks after transplantation
		M	51	Severe postoperative neuropathy and skin burns	Death within weeks of transplant due to complications including sepsis
		M	13	Massive haemolysis during surgery. Severe neuropathy	Patient at home and able to care for himself 1 year after transplant
		M	27	Severe postoperative neuropathy	Gradual recovery of muscle strength
		F	18	Minor skin burns	Good recovery after transplant
Meerman[58 104]	1994	F	34	Repeat laparotomy for postoperative bleed	Liver fibrosis present 2 years after surgery; remains well 7 years after transplant
		F	39	None	Portal fibrosis in transplant at 6 and 12 months after transplant. Liver fibrosis progressing at 7 years after transplant
de Torres[89]	1996	F	41	None	Good outcome initially, but protoporphyrin damage to transplanted liver
Lock[99]	1996	F	58	Severe polyneuropathy	Neuropathy persists 1 year after transplant, general condition markedly improved
Harper,[83] Thunell[100]	1998	M	50	Phototoxic abdominal burns, intestinal bleeding after surgery	Death from multiorgan failure 1 month after transplant
Gross[41]	1998	M	39	None	Excellent health 5 years after surgery
		M	51	Intrahepatic cholestasis	
		F	59	None	Marked improvement 1 year after surgery
		F	59	Accumulation of protoporphyrin in transplant	Post-transplant health good
		F	17	None	Good
		F	58	None	Good
		M	38	None	Good
Rüfenacht[30]	1998	F	49	Cholestasis corrected, liver function normalised	Follow-up 4 years after transplant
		F	35	Cholestasis corrected, liver function normalised	Follow-up 2 years after transplant
Nguyen[101]	1999	M	54	Polyneuropathy	Most of neuropathy had recovered 12 months after surgery
Reicheld,[65] Do[102]	1999 2002	M	55	Mild rejection episode at 3 months	Use of plasmapheresis and IV haem-albumin to protect transplanted liver
Jimenez-Saenz[103]	1999	M	59	None	Good health 30 months after transplant
Leone[105]	2000	M	35	None	Excellent health 4 years after transplant
	2000	M	50	Poor health after transplant	Died 1 month after transplant
Dellon[90]	2002	M	54	Neuropathy	Transplanted liver affected by protoporphyrin.
Schoenfeld[34]	2003	M	29	None	3 year postoperative follow-up

recommendations for optimising the environment for the transplanted liver,[58] which included the use of filtered theatre lights and short-term measures aimed at keeping the level of protoporphyrin as low as possible in the immediate post-operative period.[90 102] The introduction of such measures has reduced perioperative complications including haemolysis.[76] Furthermore, long-term use of plasmapheresis and intravenous haem-albumin has been advocated as a worthwhile therapeutic measure to prolong survival of the transplanted liver in the face of chronically raised protoporphyrin levels.[105] There are increasing reports of medium-term[30 103 105] and long-term[104] survival following EPP-related liver transplantation. However, long-term follow-up of two patients with EPP who underwent liver transplantation for acute liver failure revealed protoporphyrin deposits and onset of fibrosis in the transplanted livers 8 months and 6 months after transplantation.[104] Despite this, both patients remained in good health 7 years after surgery.[104]

ANIMAL MODELS FOR STUDY OF LIVER DISEASE IN EPP

Animal models have been used to investigate a number of therapeutic issues relating to EPP-associated liver disease. A rat liver model showed that administration of bile acids with protoporphyrin increased biliary protoporphyrin excretion, primarily by increasing the biliary protoporphyrin concentration.[107] Furthermore, chenodeoxycholic acid was found to be more effective in this regard than ursodeoxycholic acid.[108] Subsequent studies with the same model showed that high levels of protoporphyrin led to the formation of biliary thrombi in the presence of bile acids, but without significantly affecting the degree of cholestasis.[109]

The recent resurgence in animal studies in EPP has been prompted by the availability of new models of the disease and also, perhaps, by the realisation that genetic studies on patients had failed to provide answers to the key prognostic and therapeutic problems of the condition. The first mouse model of EPP was autosomal recessive, with homozygotes displaying haemolytic anaemia, photosensitivity, cholestasis and severe hepatic dysfunction.[110] Because of the severe phenotype, this model was recognised to have limited relevance to EPP in humans,[110] except in those with severe disease of autosomal recessive origin.[14] Pawliuk *et al*[111] demonstrated long-term cure of photosensitivity in murine EPP by preselective gene therapy. Ex vivo haematopoietic stem cells transduced with retrovirus expressing human *FECH* resulted in complete and long-term correction of skin photosensitivity in the transplanted mice. However, the liver damage that is invariably present in this murine model of EPP failed to improve with this treatment.[111] The exon 10-deleted mouse model for EPP demonstrates FECH activity near the threshold for phenotypic expression, which is more relevant to EPP in humans and has the potential to give insight into the contribution of genetic or environmental factors in modulating the EPP phenotype.[25]

No human gene therapy studies for EPP have been published to date, but increasing success in mouse models makes the realisation of this more likely.[112] A recent murine study described mouse recipients of bone marrow from EPP-affected mice who then developed raised erythrocyte and plasma protoporphyrin levels but with minimal skin photosensitivity and no evidence of liver damage.[113] Further murine studies with the BALB/c Fech(m1Pas) mouse model of EPP reproduces the hepatic injury seen sporadically in human EPP. Davies *et al*[114] compared this model with griseofulvin-induced hepatic protoporphyria, a model of acquired ferrochelatase injury resulting in excess protoporphyrin production. They found that the two models were associated with contrasting liver profiles for genes controlling haem synthesis and catabolism.[114] They speculated that these gene expression profiles could be used to provide candidates for human polymorphisms that explain the sporadic expression of hepatic disease in human EPP.[114] In a separate study, a mouse model has also been used to show that the genetic background modulates both anaemia and liver injury in EPP.[115]

RECOMMENDATIONS FOR MANAGEMENT OF LIVER DISEASE IN EPP

The evidence upon which recommendations for management of EPP-related liver disease are based is inconsistent. Of fundamental importance to this debate is the incidence of liver disease in EPP. It is clear that the incidence of serious liver disease in published series of patients shows wide variation, consistent with the fluctuation expected from small sampling of this type (table 2). When the data from these series are combined (with the exclusion of one highly selected series by Chen *et al*[33]), about 30 patients out of 847 (~3.5%) had severe liver disease. This incidence is higher than the frequently quoted figure of ~1%,[46] but a little lower than more contemporary estimates of ~5%.[116]

It is perhaps not surprising that, in the face of conflicting evidence, physicians caring for patients with EPP have been unable to agree on the type and level of surveillance needed to identify liver disease. Mathews-Roth[116] recommended liver biopsy in any patient with EPP whose liver function tests were even minimally abnormal, or those in whom erythrocyte and plasma porphyrins become markedly raised (red cell porphyrin >2000 μg/dl; plasma porphyrin >50 μg/ml). Mooyaart *et al*[48] measured liver biochemistry annually up to the age of 20 years and then every 2 years thereafter, and planned to carry out liver biopsies no more frequently than once every 5 years. Sarkany and Norris[60] proposed more frequent measurement of liver function tests (every 6 months) on the basis of the speed at which liver involvement can sometimes progress. Bloomer and Bonkovsky[118] advised ''close follow up'' and a liver biopsy for any patient with an unexplained abnormality in liver function and red cell porphyrin >1500 μg/100 ml (~26.7 μmol/l). Thunell *et al*[100] advised annual routine visits for biochemical assessment of liver function with referral to a hepatologist in the face of abnormal liver function, and more frequent monitoring for patients with increasing erythrocyte protoporphyrin levels above 30 μmol/l. There is currently no way of stating which of these approaches is correct, as the sensitivity of biochemical tests of liver function as a tool for diagnosing the onset of significant liver disease has never been determined. In the absence of this knowledge, histological assessment of the liver remains the gold standard with which other less invasive tests should be compared.

As highlighted earlier in this review, published genotyping data have failed to identify with absolute certainty those patients at risk of developing significant liver disease. This may be reassuring to clinicians operating in healthcare systems such as the USA and much of the developing world where ferrochelatase gene mutational analysis is not widely available. However, there appears to be an increased risk of severe liver disease in patients with null mutations[20 30–34] and in those with recessive disease.[12–14 18 23 117] It is therefore wise to regard any subject with recessive disease or who carries a null mutation as having a higher risk of liver disease. By extension, families in which one or more members have manifested EPP-related liver disease should be regarded as being potentially at higher risk,[30 119] although this higher risk is not always manifest in practice.[32 33] At the very least, the presence of EPP should be regarded as a risk factor for liver disease which should be added to other risk factors when deciding if liver biopsy is needed and can be justified.

There should be no argument about the need for liver biopsy in patients with EPP who have abnormal liver function tests or in those with acute liver decompensation. Finally, it is likely that some patients may, after frank discussion of the risk of liver disease and our current inability to predict it with

certainty, request liver biopsy in order to attain certainty and perhaps to allay anxiety. This is not unreasonable. Thus, in the absence of a clear consensus on this subject, we propose the following as indications for liver biopsy in patients with EPP:

- Patients with null mutations or autosomal recessive disease (for patients in countries where *FECH* genotyping studies are widely available).
- Patients with a family history of EPP-related liver disease.
- The presence of other risk factors for liver disease such as viral hepatitis, haemochromatosis, non-alcoholic fatty liver disease and alcohol.
- Abnormal liver function tests (although sensitivity unknown).
- Evidence for liver decompensation: sudden worsening of photosensitivity associated with rising protoporphyrin levels.
- Patient anxiety or preference.

A repeat biopsy may be necessary to assess incremental changes in patients shown initially to have early liver disease or following a change in status regarding risk factors.

In patients without an indication for immediate liver biopsy, there is still a need to provide a systematic programme of non-invasive monitoring of the liver. This might include some or all of the following:

- Investigations to exclude other causes of hepatic dysfunction such as hepatitis viral serology and tests for haemochromatosis.
- Liver function tests including aminotransferases, alkaline phosphatase and γ-glutamyl transferase.
- Red cell and plasma protoporphyrin levels.
- Measurement of hyaluronate, YKL-40, Fibrotest, Fibroscan and serum aminoterminal propeptide of type III procollagen (PIIINP) as non-specific serum markers for hepatic fibrosis.
- Ultrasound scan for gall stones.
- CT and MRI studies of the liver.

However, it should be noted that none of these tests has been adequately assessed prospectively as a tool for identification of liver disease in EPP.

CONCLUSIONS

Recent years have seen significant advances in our understanding of EPP, yet fundamental insight into the factors governing clinical expression and progression remains elusive. A review of all reported series suggests that the incidence of significant liver disease in patients with EPP is approximately 3%, although this is not truly a population-based estimate. Recent work using murine models has provided additional insights which may prove helpful in advancing more effective treatments for EPP. In particular, ex vivo haematopoietic stem cells transduced with retrovirus expressing human FECH resulted in complete and long-term correction of skin photosensitivity in transplanted mice.[111] A bone marrow transplant resulted in cure of symptoms of EPP; interestingly, transplantation was indicated for acute myelogenous leukaemia rather than the coexisting autosomal recessive EPP, which was in fact previously undiagnosed.[117] A recent report on 20 patients with EPP who underwent liver transplantation, in most of whom liver disease recurred, led the authors to stress the importance of considering bone marrow transplantation in liver transplant recipients in order to forestall this.[84] However, the risks inherent in allogeneic bone marrow transplantation make this an unattractive option for the prevention of EPP-associated liver disease. It is not unrealistic to anticipate future correction of the protoporphyria phenotype by autologous transplantation of haematopoietic stem cells transfected in vitro with normal *FECH* DNA.

Until better evidence is available on the optimal method for detecting liver disease in EPP, clinicians caring for patients with EPP should remain vigilant and make an individualised assessment of risk based on the factors listed above, rather than relying arbitrarily on a standard set of tests to determine the need for liver biopsy or for specific therapeutic interventions. The consequences of EPP-related liver disease are sufficiently serious to justify every effort being made to prevent factors with the potential to exacerbate cholestasis. Thus, alcohol should be avoided altogether, and all patients with EPP should be vaccinated against hepatitis A and B. Where the risk is believed to be high, a liver biopsy is mandatory. Because of the specialised nature of this problem, there are significant advantages to patients with EPP if hepatic monitoring is carried out in collaboration with an experienced hepatologist.

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EDITOR'S QUIZ: GI SNAPSHOT

Answer

From question on page 967

CT demonstrated all essential features of gastroduodenal intussusception—namely (1) invagination of the pyloric part of the stomach into the duodenum, which gives a "beak" appearance (fig 1A); (2) classical target sign or bull's eye appearance, which consists of concentric circles of low and high densities (fig 1B); and (3) a roundish mass with fat density, which serves as a lead point (fig 1C).

Both oesophagogastroduodenoscopy (fig 2) and laparoscopy confirmed the presence of gastroduodenal intussusception, which was reduced by both endoscopic gas insufflation and laparoscopic manipulation. The duodenal tumour was resected through a longitudinal gastroduodenostomy and was confirmed histologically to be submucosal lipoma.

Intussusception is most frequently seen in children. Adult cases are invariably associated with a lead point, which can be a benign or malignant tumour. The most common site of intussusception is either the small or large bowel. Gastroduodenal intussusception due to duodenal lipoma is extremely rare and may present as gastric outlet obstruction and occult blood loss due to formation of surface ulcers.

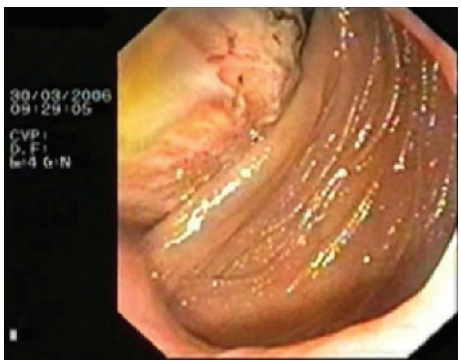

Figure 1 Endoscopy showing the duodenal submucosal lipoma and surface ulcer. The pylorus invaginated into the second part of duodenum (presence of circular folds).

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