composed at least in part of protoporphyrin occur in some patients. Hepatic complications appear to be higher in autosomal recessive EPP due to two *FECH* mutations and in XLP.

Diagnosis A substantial increase in erythrocyte protoporphyrin, which is predominantly free and not complexed with zinc, is the hallmark of EPP. Protoporphyrin levels are also variably increased in bone marrow, plasma, bile, and feces. Erythrocyte protoporphyrin concentrations are increased in other conditions such as lead poisoning, iron deficiency, various hemolytic disorders, all homozygous forms of other porphyrias, and sometimes even in acute porphyrias. In all these conditions, however, in contrast to EPP, protoporphyrin is complexed with zinc. Therefore, after an increase in erythrocyte protoporphyrin is found in a suspected EPP patient, it is important to confirm the diagnosis by an assay that distinguishes free and zinc-complexed protoporphyrin. Erythrocytes in EPP also exhibit red fluorescence under a fluorescence microscopy at 620 nm. Urinary levels of porphyrins and porphyrin precursors are normal. Ferrochelatase activity in cultured lymphocytes or fibroblasts is decreased. DNA diagnosis by mutation analysis is recommended to detect the causative *FECH* mutation(s) and/or the presence of the IVS3–48T>C low expression allele. To date, over 190 mutations have been identified in the *FECH* gene, many of which result in an unstable or absent enzyme protein (null alleles) (Human Gene Mutation Database; *www.hgmd.org*). Studies suggest that EPP patients with a null allele (and the IVS3–48T>C low expression allele) have a greater risk for developing severe liver complications.

In XLP, the erythrocyte protoporphyrin levels appear to be higher than other forms of EPP and the proportions of free and zinc protopophyrins may reach 50%. To date, four *ALAS2* mutations, three deletions of one to four bases, and one novel nonsense mutation have been described, which markedly increase ALA synthase 2 activity and cause XLP. XLP accounts for about 2% of patients with the EPP phenotype in Western Europe. Recent studies show that about 10% of North American patients with the EPP phenotype have XLP.

TREATMENT ERYTHROPOIETIC PROTOPORPHYRIA

Avoiding sunlight exposure and wearing clothing designed to provide protection for conditions with chronic photosensitivity are essential. Oral β-carotene (120–180 mg/dL) may improve tolerance to sunlight in some patients. The beneficial effects of β-carotene may involve quenching of singlet oxygen or free radicals. The dosage may need to be adjusted to maintain serum carotene levels in the recommended range of 10–15 mmol/L (600–800 mg/dL). Mild skin discoloration due to carotenemia is the only significant side effect. Afamelanotide, an α-melanocyte-stimulating hormone (MSH) analogue has completed phase III clinical trials in the United States for patients with EPP and XLP.

Treatment of hepatic complications, which may be accompanied by motor neuropathy, is difficult. Cholestyramine and other porphyrin absorbents such as activated charcoal may interrupt the enterohepatic circulation of protoporphyrin and promote its fecal excretion, leading to some improvement. Splenectomy may be helpful when the disease is accompanied by hemolysis and significant splenomegaly. Plasmapheresis and intravenous hemin are sometimes beneficial.

Liver transplantation has been carried out in some EPP and XLP patients with severe liver complications and is often successful in the short term. However, the disease often recurs in the transplanted liver due to continued bone marrow production of excess protoporphyrin. In a retrospective study of 17 liver-transplanted EPP patients, 11 (65%) had recurrent EPP liver disease. Posttransplantation treatment with hematin and plasmapheresis should be considered to prevent the recurrence of liver disease. However, bone marrow transplantation, which has been successful in human EPP and which prevented liver disease in a mouse model, should be considered after liver transplantation, if a suitable donor can be found.

Acknowledgment

The authors thank Dr. Karl E. Anderson for his review of the manuscript and helpful comments and suggestions. This work is supported in part by the Porphyrias Consortium (U54 DK083909), a part of the National Institutes of Health (NIH) Rare Disease Clinical Research Network (RDCRN), supported through collaboration between the NIH Office of Rare Diseases Research (ORDR) at the National Center for Advancing Translational Science (NCATS), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. MB is supported by a career development award K23-DK-095946