Erythropoietic Protoporphyria and Terminal Hepatic Failure

DANIELA BRUCH-GERHARZ1, KLAUS BOLSEN1, CLAUS-DIETER GERHARZ2 and GÜNTHER GÖRZ1
Departments of 1Dermatology and 2Pathology, Heinrich-Heine-University of Duesseldorf, Germany

We report on a 44-year-old patient with erythropoietic protoporphyria who could effectively control his photosensitivity for 22 years with oral carotenoids. The clinical course of his disorder was complicated by liver involvement, initially expressed as marginally raised serum transaminase levels for several years. Terminal hepatic failure with fatal outcome developed 22 years after manifestation of his liver function abnormalities. Hepatic involvement represents an inconsistent and unpredictable feature of erythropoietic protoporphyria, determining the prognosis of an otherwise clinically benign disorder. Key words: liver; porphyrins; photosensitivity; ferrochelatase.

(Accepted February 6, 1996.)


D. Bruch-Gerharz, M.D., Department of Dermatology, Heinrich-Heine-University of Duesseldorf, P.O. Box 101007, D-40001 Duesseldorf, Germany.

Erythropoietic protoporphyria (EPP) is a hereditary disorder of porphyrin metabolism characterized by a decreased activity of the mitochondrial enzyme ferrochelatase (FeCh) and excessive concentrations of protoporphyrin in red blood cells, plasma, bile and feces (1, 2). Until recently, this condition was thought to be inherited as an autosomal dominant trait with variable penetrance (3); recent data, however, suggest an autosomal recessive mode of inheritance in some cases (4).

EPP patients usually present with a history of disabling photosensitivity, with both acute phototoxic skin reactions and chronic haemolysis-like cutaneous lesions at the light-exposed areas due to photoexcitation of protoporphyrin by UVA and visible light. Most cases manifest in early childhood after the first longstanding exposure to sunlight; the clinical features, thereafter, tend to aggravate in spring and summer (5).

The liver is occasionally affected in EPP and reveals a spectrum of histopathologic features ranging from moderate inflammation to fibrosis. Nearly all EPP patients suffer from cholelithiasis, but only rarely is serious liver disease recorded, culminating in fatal liver cirrhosis (6). Therefore, it has been hypothesized that protoporphyrin exerts a light-independent toxic effect on the liver; nevertheless, the exact pathophysiological mechanisms underlying progressive liver damage are still incompletely understood (7).

We report on an EPP patient with terminal hepatic failure 22 years after manifestation of his liver dysfunction. The insidious evolution of hepatic failure observed in our patient emphasizes the potentially fatal role of liver complications in patients with EPP.

CASE REPORT

EPP was first diagnosed in our patient in 1971 at the age of 22 years. Since early childhood the patient had experienced moderate cutaneous photosensitivity, characterized by burning and painful discomfort followed by a transient erythema of sun-exposed skin. Episodes typically occurred in spring and summer, with the skin lesions and symptoms becoming apparent within minutes or hours subsequent to sun exposure. Family history revealed only a half-brother with similar skin changes and solar intolerance. The other family members had no evidence or history of a photodermatosis or porphyria.

At his first presentation in our clinic in 1971, the 22-year-old patient exhibited erythematous phototoxic skin reactions on the dorsal aspects of both hands and forearms, lichenified haemolysis cutis-like lesions on the dorsa of his hands, and fingers (Fig. 1b), as well as pseudohydrates surrounding the vermilion border. Elevated protoporphyrin concentrations in erythrocytes were demonstrated by porphyrin analysis (2700 nmol/dl; normal, <72). Fluorescence microscopic examination revealed orange-red fluorescence of red blood cells, the so-called fluorocytes (Fig. 1c).

Blood cell count was normal, whereas routinely performed laboratory investigations revealed normal values for AST (32 U/l; normal, <18), ALT (36 U/l; normal, <22) and total serum bilirubin (1.48 mg/dl; normal, <1.2). Moderately increased serum transaminase levels had already been observed at the age of 18 years for the first time.

Carotinoid therapy (daily oral doses of 75–150 mg beta-carotene or carthamins) provided effective photoprotection. Repeated controls of liver function revealed no abnormalities, although the patient reported intermittent alcohol abuse since 1979.

During the next 15 years the patient was not available for follow-up until he was readmitted to our Department in 1994. On examination, the 44-year-old patient revealed marked jaundice, as well as peripheral oedemas, enlarged liver at palpation and venous collaterals, indicating severe hepatic insufficiency. Laboratory investigations showed increased levels of serum alkaline phosphatase (464 U/l; normal, 65 to 220), AST (253 U/l) and a mild iron deficiency anemia (hemoglobin 10.3 g/dl; normal, 12 to 16) and elevated IgG level. Antinuclear antibodies (ANA), hepatitis antigens and antibodies were negative. The patient showed markedly increased erythrocyte porphyrin concentrations (5135 nmol/dl), a FeCh activity in leucocytes reduced to approximately 20% of normal, elevated total bilirubin levels (13.5 mg/dl) as well as hyperammonemia (484 µg/dl; normal, 15 to 60). Abdominal ultrasonography revealed liver cirrhosis, splenomegaly, an 8 mm in diameter gallstone in the gall-bladder, but no evidence of biliary tract obstruction. Severe phototoxic skin reactions could be demonstrated in chronically light-exposed areas, such as the dorsa of the hands (Fig. 1d). The patient reported an increase of phototoxity in parallel to the progression of his liver disease.

The liver function continued to deteriorate during the next days, and the patient died after an acute hemorrhage from esophageal varices. Autopsy revealed cholestatic cholangitis and a black stained liver with cirrhosis (Fig. 2a). Histological evaluation showed complete cirrhosis (Fig. 2b) with foci of hepatocellular necrosis and Mallory bodies (Fig. 2c), compatible with ethanol-induced injury. In addition, there was an excessive accumulation of red-brown pigment within Kupffer cells, hepaticocytes and bile canaliculi. Polarization showed this pigment to be red birefringent (Fig. 2d), and crystalline-like configurations could be identified. Ultrastructural examination of liver specimens revealed aggregates of crystalline structures that were straight or slightly curved and erratically arranged in the cytoplasm of hepaticocytes (Fig. 2e,f). Finally, the postmortem liver specimen contained 483 nmol protoporphyrin/g liver, i.e. a 150-fold increased concentration in comparison to normal liver.

DISCUSSION

Although EPP is generally regarded as a benign metabolic disorder, it may occasionally be associated with severe,
progressive and fatal liver injury. Unfortunately, our patient was not available for follow-up for 15 years prior to the manifestation of his liver failure. Thus, a therapeutic intervention with chenodeoxycholic acid or cholestyramine was not possible.

Histopathological examination of liver biopsies from EPP patients with overt liver disease reveals inflammation and fibrosis extending from the portal areas as well as bile thrombi indicative for cholestasis. Furthermore, granular deposits of protoporphyrid birefringent upon examination with polarized light can be found in hepatic parenchymal cells, Kupffer cells and bile duct epithelia. Ultrastructurally, they appear as slightly curved crystals, often arranged in typical rosettes within phagolysosomes (8, 9). Interestingly, the protoporphyrid deposits can also be demonstrated in the liver cells of patients without apparent liver abnormalities (10). Ongoing liver damage finally results in micronodular cirrhosis with loss of normal architecture and cholestasis. In our patient, however, chronic alcohol abuse had most probably contributed to the progression of liver injury.

The pathophysiological mechanisms of liver injury in EPP are still a matter of controversy. Clinicopathological and experimental studies indicate that liver damage in EPP is associated with an accumulation of protoporphyrid in hepatobiliary structures (11), resulting in a light-independent formation of active oxygen species, which in turn cause toxic damage to hepatic tissue (5). The role of the liver itself as a production site of protoporphyrid in EPP, however, has not yet conclusively been elucidated, since the erythropoietic and hepatic production of protoporphyrid cannot be quantitated separately (12). Hepatic protoporphyrid production has been suspected in only a few reports on EPP (13, 14), whereas most clinical and experimental observations suggest that the erythropoietic tissue is the major source of excessive protoporphyrid (15–19).

Analysis of porphyrin metabolism after liver transplantation in EPP patients could give some insight into the role of the liver in the production of protoporphyrid. Indeed, the transplanted liver has normal FeCh activity and cannot, therefore, produce increased amounts of protoporphyrid. Thus, a long-term follow-up of liver transplant recipients could greatly contribute to a better understanding of the pathogenesis of progressive liver disease in EPP. Unfortunately, reports on liver transplantation in EPP patients so far only present data on porphyrin metabolism obtained shortly after liver transplantation (16–22). These short-term data on porphyrin metabolism, however, are blurred by the effects of massive blood transfusion prior to and during liver transplantation, which per se reduces the mean level of erythrocyte protoporphyrid concentration.

It is currently impossible to make any reliable prediction of the individual risk of an EPP patient for the development of hepatic failure. In view of the poor prognosis of clinically
overt liver disease and the risks of liver transplantation (20–22), EPP patients should have regular liver function tests and periodic liver biopsies that might permit earlier recognition of progressive liver damage, so that prophylactic treatment could be initiated.

ACKNOWLEDGEMENT

We are indebted to Prof. Dr. Tsambouros, University of Patras, Greece, for critical reading of the manuscript.

REFERENCES


Acta Derm Venereol (Stockh) 76