The Diagnosis and Management of Erythropoietic Protoporphyria

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Abstract: Porphyrias are a group of metabolic disorders resulting from enzymatic defects in the heme biosynthetic pathway. Erythropoietic protoporphyria is thought to be the second most common porphyria seen in clinical practice. It is, however, commonly underrecognized and can lead to both cutaneous manifestations as well as derangement in hepatic function in a minority of patients. This review summarizes the current understanding of this disorder. Different treatment options are discussed with the goal of preventing liver damage. The roles of liver and bone marrow transplantation are also addressed.

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Porphyrias are a group of metabolic disorders caused by defects in the heme biosynthetic pathway. Heme is the critical prosthetic group for numerous hemoproteins such as hemoglobin, myoglobin, catalase, and microsomal cytochromes. The term "porphyria" is derived from the Greek word "porphyra," which means "purple." The biochemical hallmark of porphyrias is overproduction and, ultimately, overexcretion of compounds called porphyrins, which have a deep red or purple color. The first clinical reports of porphyria appeared in the late nineteenth century and described a patient with severe cutaneous photosensitivity and brown pigmentation of the bones, which is characteristic of congenital erythropoietic porphyria. Soon thereafter, a case of acute porphyria was described in a person addicted to drugs who had urine the color of port wine and later died after taking the hypnotic drug sulfonomethane.

Porphyrias can present clinically either with neurovisceral symptoms and signs such as abdominal pain, constipation, and weakness or with cutaneous symptoms and signs. In hereditary coproporphyria and variegate porphyria, patients may present with both types of symptoms; in the other forms of porphyria, patients manifest only one type of clinical presentation. When considering therapy for porphyrias, it is useful to classify the disorders into two major categories: acute/inducible porphyrias or chronic cutaneous porphyrias (Table 1). Regardless of the specific type of acute porphyria or associated enzymatic defect, all of the acute porphyrias produce similar neurovisceral manifestations and should be managed in a similar manner. Management of cutaneous porphyria,

Table 1. Classification and Major Features of Human Porphyrias

Disease	Primary enzymatic defect	Autosomal inheritance	Clinical features	
			Neurovisceral symptoms	*Photosensitivity dermatosis*
Acute/inducible porphyrias				
ALA-D deficiency porphyria	ALA dehydratase	Recessive	+	--
Acute intermittent porphyria	PBG deaminase	Dominant	+	--
Hereditary coproporphyria	Coproporphyrinogen oxidase	Dominant	+	+
Variegate porphyria	Protoporphyrinogen oxidase	Dominant	+	+
Chronic cutaneous porphyrias				
Congenital erythropoietic	Uroporphyrinogen III cosynthase	Recessive	--	++
Hepatoerythropoietic porphyria	Uroporphyrinogen decarboxylase	Recessive	+/-	+
Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	Dominant (acquired variant exists)	--	+
Protoporphyria	Ferrochelatase	Dominant†	--*	+

ALA=5-aminolevulinate; ALA-D=ALA dehydratase; PBG=porphobilinogen. ALA is the first intermediate in the heme biosynthetic pathway, and PBG is the second intermediate in the heme biosynthetic pathway.

*A neurovisceral syndrome reminiscent of those observed in acute porphyrias has been described in several patients with protoporphyria and hepatic failure around the time of orthotopic liver transplantation; †autosomal recessive inheritance has been described.

though more specific to the particular type of porphyria, also involves the application of several general principles.

Enzymatic Defects and Genetics

Erythropoietic protoporphyria (EPP) was first described by Magnus and associates in 1961.[1] Bonkovsky and colleagues demonstrated that heme synthase or ferrochelatase (FECH), an inner mitochondrial enzyme, was deficient in this disorder (Figure 1).[2] Since then, the gene for FECH has been localized to 18q21,[3,4] and approximately 120 disease-producing mutations have been described to date. The gene has 11 exons and a minimum size of 45 kb. From early studies of kindreds with EPP, most investigators concluded that the disease displayed autosomal dominant inheritance with low penetrance and an increased propensity to develop chronic liver disease,[5] though autosomal recessive forms of EPP have also been described.[6] The activity of ferrochelatase in clinically affected patients is approximately 15–25% of normal activity. The parents of many patients are asymptomatic and phenotypically normal, though approximately one half demonstrate decreases in ferrochelatase activity. More recent familial studies have identified a single nucleotide polymorphism (IVS3-48C), which leads to a lower level of expression of the normal FECH gene allele.[7] Patients develop clinical disease with less than 25% of normal FECH activity when a mutated allele is inherited along with the low-level–expressing, wild-type allele, which usually harbors the IVS3-48C polymorphism. One recent paper stressed the importance of large deletions in the FECH gene exons as an important cause of "mutation-negative" EPP.[8]

FECH carries out the ultimate step in heme biosynthesis, namely the insertion of ferrous iron into protoporphyrin for the formation of heme. The only difference between heme and protoporphyrin is the insertion of an iron atom into the tetrapyrrole ring in heme. This insertion increases the stability of the structure and results in the loss of its fluorescent properties. In EPP, the major site of protoporphyrin overproduction is localized to the bone marrow, where erythrocytes are developed.[9-12] Protoporphyrin, unlike other porphyrins, is water-insoluble and therefore removed from the body only through hepatic excretion into bile or feces. Protoporphyrin is not excreted in urine, though it does undergo some enterohepatic circulation.

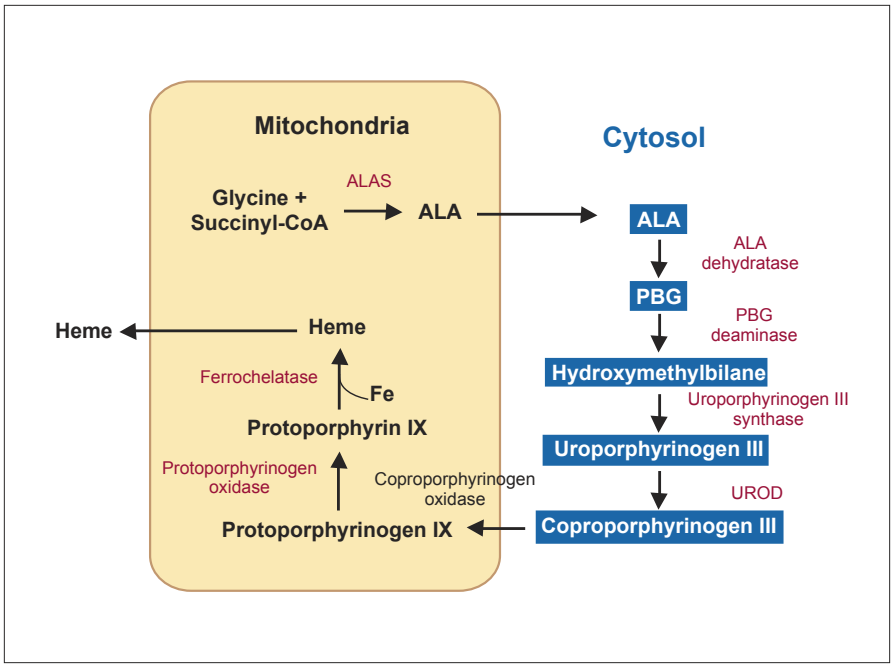

Figure 1. The heme biosynthetic pathway.

ALA=5-aminolevulinate; ALAS=delta-aminolevulinate synthase; PBG=porphobilinogen; UROD=uroporphyrinogen decarboxylase.

Epidemiology and Clinical Presentation

Of all the porphyrias found in the United States, EPP is thought to be second in prevalence only to porphyria cutanea tarda. The exact prevalence of EPP has not been reliably estimated due to its frequently mild nature and normal urinary porphyrins, which increase the possibility of missing bona fide cases. There is no gender predominance in EPP, which is found across all ethnic and racial groups.

EPP, a disorder with highly variable clinical expression, has been previously well characterized as a chronic cutaneous porphyria.[13-16] Most affected patients present in early childhood with sun sensitivity and, at times, an urticarial-type reaction. Infants and children classically develop intense burning pain from sun-exposed skin following brief exposure in the spring and summer. Several hours later, erythema, edema, and itching become prominent. Vesicles are uncommon and develop only with prolonged sun exposure. With chronic and repeated exposure, involved skin may become leathery and hyperkeratotic. This reaction is particularly prominent in a malar "butterfly" pattern on the face and over the knuckles of the hands. Patients usually have a chronic and stable disease course, with no identified aggravating factors.

Photoactivation of lipid-soluble protoporphyrin, which is deposited in the dermal blood vessels, leads to the characteristic skin burning from sun exposure. Chronic facial scarring, hirsutism, and fluorescent teeth, which are common in congenital erythropoietic porphyria or hepatoerythropoietic porphyria, are not usually found in EPP.[16] Photoactivation of circulating water-soluble uroporphyrins, on the other hand, leads to chronic blistering, as seen in congenital erythropoietic porphyria and porphyria cutanea tarda.

The most serious complication of EPP is development of pigmentary cirrhosis of the liver.[17,18] Fortunately, liver injury is evident in only a minority of patients with EPP (~10%), with approximately 3–5% of the patients eventually developing end-stage liver disease. The pattern of liver injury, when seen in this disorder, typically develops over a period of time and ranges from mild liver disease with elevations in liver enzymes to progressive liver disease with extensive bridging fibrosis or cirrhosis and other concomitant complications. By itself, EPP rarely presents as true acute liver injury, though there may be sudden acute worsening of underlying chronic liver disease.[19] Liver disease is thought to develop due to the precipitation of protoporphyrin in hepatocytes and biliary radicles.[20,21] No risk factors have been identified that are able to predict the development of liver disease in EPP thus far.

A common complication of EPP is the development of pigment gallstones, which have a high content of protoporphyrin. In bile, protoporphyrin may crystallize, providing the nidus for development of gallstones. When evident in children, gallstones should prompt evaluation for EPP.[22] Mild anemia with or without hemoly-

sis is occasionally noted. In EPP, abdominal pain and neuropathy-like symptoms are seen only rarely and in the setting of advanced liver disease.[23-26] Of note, motor neuropathy can develop both pre- and postoperatively at the time of liver transplantation.

Diagnosis

The diagnosis of EPP requires the demonstration of increased levels of protoporphyrin, without increased levels of coproporphyrin, in the stool, RBCs, or both.[27] In EPP, elevated levels of erythrocyte protoporphyrin, plasma protoporphyrin, and stool protoporphyrin are evident. Urinary porphyrin levels are usually normal because, as already mentioned, protoporphyrin is not excreted into the urine. Analysis of the plasma porphyrin emission spectrum reveals a characteristic peak at approximately 634–636 nm, following excitation with light in the Soret band (~400 nm). Erythrocyte protoporphyrin elevations are also evident in severe iron deficiency and lead poisoning. In EPP, the protoporphyrin is primarily free protoporphyrin, in contrast to iron and lead toxicity, in which predominantly Zn-protoporphyrin is found.[28] In EPP patients, rising plasma protoporphyrin levels, along with severe elevations in RBC protoporphyrin levels, may portend impending liver failure.[29,30] Patients with EPP who develop significant liver disease have been shown to have significant increases in urinary coproporphyrin levels. An inversion of the physiological urinary coproporphyrin isomer III/I ratio has also been observed in patients with protoporphyria who develop cholestatic cirrhosis.[31] Liver biopsy is performed to assess the severity of suspected liver disease, particularly in patients with very high RBC (>5,000 μg/dL) or plasma protoporphyrin (>1,000 μg/dL) concentrations. Polarized microscopy of the biopsy may demonstrate birefringent crystal deposits with characteristic Maltese cross patterns in EPP. Plugging of biliary canaliculi with protoporphyrin may also be evident in patients with advanced liver disease.[32]

Management

A multitude of treatment options are available for EPP,[27] ranging from efforts to reduce protoporphyrin overproduction in the bone marrow to augmenting its excretion into bile (Table 2). Other agents are used for their cytoprotective properties in conjunction with measures to reduce the circulating pool of protoporphyrin and, on occasion, liver transplantation to correct end-organ damage. Cutaneous protection with opaque sunscreens and barrier clothing cannot be overemphasized. Standard sunscreens are not useful; the only topical sunscreens that are effective at blocking wavelengths greater than 400 nm, with a high sun protection factor (>30), are light-opaque, contain zinc oxide or titanium dioxide, and may be cosmetically unacceptable to some patients. Oral beta-carotene (Solatene, Roche; 60–180 mg orally per day) reduces photosensitivity in approximately 80% of patients over a 1–3 month period after initiation of therapy. Beta-carotene causes yellow-orange discoloration of the skin, and topical beta-carotene cream is ineffective. Beta-carotene is thought to scavenge the free radicals generated by the excitation of protoporphyrin and is dosed to maintain a therapeutic serum level of 600–800 μg/dL.[33] Beta-carotene's efficacy has been questioned in the recent literature, and many patients have found their resulting yellow skin difficult to accept. Oral cysteine has also been used and is thought to have a similar mechanism of action.[34] Bile-acid binding agents such as cholestyramine[35,36] have been used to decrease the enterohepatic circulation of protoporphyrin. Patients have attempted to use long-term activated charcoal as a safe and cheap alternative in the hopes of decreasing intestinal reabsorption of protoporphyrin.[37] Intravenous vitamin E was reported in a case report as being effective for reversing liver disease.[38] Ursodeoxycholic acid has been used in patients with early liver disease,[31] not only because of its ability to enhance the biliary excretion of protoporphyrin, but also because of its cytoprotective properties.[39-41] However, a recent study in an autosomal recessive mouse model of EPP demonstrated no benefit with the use of ursodeoxycholic acid and heme arginate.[42] Patients are advised against caloric restriction and should undergo iron replacement only if they are found to be iron-deficient.[43-47]

Chronic therapy with intravenous hematin and erythrocyte transfusions is thought to suppress heme

Table 2. Targets for Intervention

- **Increase protoporphyrin excretion into bile:** ursodeoxycholic acid
- **Reduce protoporphyrin production:** hematin and red blood cell transfusion
- **Decrease the circulating pool of protoporphyrin**
  - **Removal:** plasmapheresis, hemodialysis, and exchange transfusions
  - **Interrupting enterohepatic circulation:** cholestyramine and activated charcoal
- **Use antioxidants or cytoprotective agents:** vitamin E and ursodeoxycholic acid
- **Perform liver transplantation**
- **Correct the underlying defect:** bone marrow transplantation

production[48-51] by decreasing protoporphyrin levels. Exchange transfusions and plasmapheresis have been used to remove the protoporphyrin in transit, as a bridge to liver transplantation or other more definitive treatments. Heme therapy, along with plasmapheresis, has been noted to stabilize patients with advanced liver disease.[52-54] Nonbiologic liver assist devices have been used recently in an attempt to decrease the morbidity associated with motor neuropathy, both in the pre- and postoperative period.[55]

Since the first liver transplantation for EPP-related liver disease in 1980, EPP patients with progressive liver disease have been transplanted with acceptable outcomes. Liver transplant recipients from US centers have been shown to have 1-, 5-, and 10-year survival rates of 85%, 69%, and 47%, respectively.[56] These survival rates are similar to those for liver transplants performed for other indications. However, recurrent EPP was found in 65% (11/17) of patients who survived more than 2 months post-transplant. The high incidence of recurrent disease post-transplant is not surprising, as the transplant itself does not correct the primary cause and major source of protoporphyrin overproduction, which has been shown to be in the bone marrow.[57] Of all the porphyrias, EPP has the best established indication for liver transplantation as a therapeutic option.[58] The previous medical literature, as well as more recent reports, have demonstrated a benefit in EPP patients who receive a bone marrow transplant.[59,60] Successful bone marrow transplantation with or without liver transplantation, depending upon the severity of the liver disease, is considered the definitive treatment for EPP.

Patients with EPP are at increased risk of developing chronic liver disease and should be vaccinated for hepatitis A and B (and possibly hepatitis E in the near future) in case they are found not to be immune. They should be counseled to avoid hepatotoxins such as alcohol because of the risk of accelerating their liver disease.[61] EPP patients with no evident liver disease should be monitored with liver enzymes and porphyrin levels, both serum and RBC protoporphyrin, at least every 6 months, if not more frequently, to detect early signs of liver injury.[62] Patients with known chronic liver disease should also be screened regularly for hepatocellular carcinoma.

Effective management of EPP involves the judicious use of all available treatment options to prevent disease progression and possibly achieve cure. Treatment is directed at minimizing complications from sun damage, monitoring for development of liver disease, and stabilizing cholestatic liver disease once it develops, in the hopes of a more definitive treatment such as bone marrow transplantation with or without liver transplantation. The initial experience with bone marrow transplantation is promising, though the opportune moment to intervene remains unclear.

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