ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Overview of Liver Involvement in Patients With Erythropoietic Protoporphyria

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G&H How does erythropoietic protoporphyria differ from other porphyrias, and what are its most common signs and symptoms?

CL Erythropoietic protoporphyria (EPP) is a rare genetic disease that results from pathogenic variants in both *FECH* alleles, leading to a deficiency in the level of the enzyme ferrochelatase. Unlike acute hepatic porphyrias, EPP does not have classic neurovisceral involvement. Characterized by significant cutaneous phototoxicity, EPP is a nonblistering type of porphyria, unlike porphyria cutanea tarda, which causes blisters with sun exposure.

EPP usually presents in very early childhood. However, there is typically a delay of several years between the beginning of clinical symptoms and diagnosis because of inadequate awareness of the disease. The average age of symptom onset is 3 to 4 years of age, but the median age of diagnosis is in the early teenage years.

Because ferrochelatase is the last enzyme in heme biosynthesis, deficiency of the enzyme results in the accumulation of protoporphyrin, which is hydrophobic and deposited in lipid layers of cell membranes. Exposure to visible light photoactivates protoporphyrin, causing the formation of reactive oxygen species and, consequently, severe and painful cutaneous phototoxic reactions. After a given period of exposure to sunlight, patients receive warning signs (eg, tingling or mild burning sensations) to move away from the sunlight. If sunlight exposure persists, patients experience a very painful reaction that can last for 2 to 3 days and is very difficult to manage. On average, patients can usually tolerate less than 30 minutes of sunlight, but that is highly variable. Therefore, patients manage their condition by carefully protecting themselves from sunlight (eg, with long-sleeve shirts, hats, gloves, zinc-containing sunscreen), and often try to completely avoid sunlight, which severely affects their quality of life.

For the vast majority of patients, EPP does not affect survival. However, a small subset can develop severe liver involvement, which may evolve into a life-threatening situation.

G&H How and why can the liver be involved?

CL Much is still unknown regarding hepatobiliary involvement in EPP and the other type of protoporphyria, X-linked protoporphyria (XLP), which is even rarer. (Clinically, both types of protoporphyria manifest the same way.) In cross-sectional studies of patients with EPP and XLP, up to 25% reported having had an elevation in liver enzymes. Whether that elevation was owing to porphyria or to another cause was not investigated. However, a recent cohort study from the Netherlands reported only 6.2% of patients having elevations greater than 2 times the upper limit of normal. In this study, among patients with available transient elastography results, 29% had increased controlled attenuation parameter suggestive of steatosis and 10 patients (9.6%) had increased liver stiffness scores greater than 7.2 kPa (with 7 patients classified as having F2 and 3 patients as having F3).

In addition, it is very common for these patients to have gallstones because protoporphyrin is insoluble and crystallizes in bile, resulting in inspissated and toxic bile

as well as the formation of gallstones that are rich in protoporphyrin. Studies suggest that 25% to 30% of patients with EPP and XLP have gallstone disease, and high rates of cholecystectomy are reported in this population.

A small minority of patients with protoporphyria (2%-5%) can develop a very severe, rapidly progressing form of liver involvement known as protoporphyric hepatopathy, with acute right upper quadrant abdominal pain, jaundice, and significant liver dysfunction, culminating in liver failure. Milder cases lead to chronic hepatopathy, which can progress more slowly toward cirrhosis and end-stage liver disease. Because this is a rare complication not commonly detected at earlier stages, little is known about the natural history of the disease.

> Even though only a minority of patients with EPP are at risk for liver disease, it is recommended that all patients undergo routine testing for liver chemistries at the time of diagnosis and annually thereafter.

The pathogenesis of liver disease in EPP is not well understood. However, it is known that metal-free protoporphyrin is produced by bone marrow reticulocytes, accumulates in circulating erythrocytes, and diffuses into plasma. When protoporphyrin reaches the liver, it is taken up by hepatocytes and tends to accumulate. When the level of protoporphyrin reaches an excess (although the exact level is not known), there is spillage of protoporphyrin into the bile canaliculi through the efflux receptor ABCG2. It is thought that once protoporphyrin reaches the small bowel, it undergoes enterohepatic circulation.

When in contact with cholangiocytes, this toxic bile causes cytotoxicity through production of reactive oxygen species, lipid peroxidation, and membrane damage. Eventually, this leads to cholestasis, fibrosis, and progression to end-stage liver disease.

G&H Are there risk factors for the development of liver disease in patients with EPP?

CL More research is needed owing to a lack of well-designed natural history studies in patients with EPP. Certain pathogenic variants are more likely to be associated with protoporphyric hepatopathy. It is also likely that other factors that injure the liver (eg, viral infection, toxins such as alcohol) can predispose patients to disease progression. The higher the levels of protoporphyrin, the higher the likelihood these patients can have liver involvement.

G&H How can liver involvement be monitored in patients with EPP?

CL Even though only a minority of patients with EPP are at risk for liver disease, it is recommended that all patients undergo routine testing for liver chemistries at the time of diagnosis and annually thereafter. If liver chemistries are normal, no further action is taken. If there is liver enzyme elevation, further investigation is needed to exclude other causes (eg, viral hepatitis, autoimmune conditions, other genetic diseases), as is recommended for any patient with a liver chemistry abnormality. In addition, an elevation in liver enzymes is an indication to evaluate liver and spleen morphology with an abdominal ultrasound. Protoporphyrin levels need to be monitored serially (likely annually). Liver elastography should be considered, although data are limited on its role in EPP, and clinicians may have a lower threshold for obtaining a liver biopsy. Given the rarity of EPP, it is also important to consider referring patients to an expert in porphyria for management of the condition.

G&H How should patients with EPP and mild liver involvement be treated?

CL If a patient has mild to moderate elevation of liver enzymes or any degree of liver dysfunction, medical management should be considered. Because there have been no clinical trials, recommendations are based upon small case series or case reports. One agent that has been used in patients with EPP and liver dysfunction is ursodeoxycholic acid. This agent can improve the solubility of the bile and make it more hydrophilic and less toxic.

Once protoporphyrin is in the liver and is secreted in bile, it undergoes enterohepatic circulation. It has been suggested that using a bile acid–binding resin such as cholestyramine can interrupt the enterohepatic circulation of protoporphyrins and decrease the level of protoporphyrin in the liver, potentially decreasing cytotoxicity. There have been reports of improvements in liver chemistries with cholestyramine in this population. Therefore, a combination of ursodeoxycholic acid with cholestyramine is usually recommended when patients with EPP have elevated liver enzymes. Patients should avoid alcohol use in this situation. Oral contraceptives can be used, but

low-dose estrogen is recommended to avoid any potential drug-induced hepatotoxicity with cholestasis that could confound or worsen liver disease.

G&H How should patients with EPP who present with advanced liver disease or liver failure be managed?

CL As mentioned previously, a small subset of patients present with very advanced liver disease and even liver failure. For those patients, liver transplant should be considered as a temporizing measure. It cannot cure the disease; it just induces a temporary remission. Liver transplant should be performed in a center with expertise in the treatment of porphyrias and that can also perform other specialized treatments recommended for these patients. Liver transplant has been performed in a number of patients with EPP, with long-term outcomes that are comparable with its performance for other liver diseases.

In addition, there are some specific risks associated with liver transplant for patients with EPP. For instance, patients with EPP have very high plasma levels of protoporphyrin at that point and are thus very photosensitive. The lights in the operating room can cause significant burns on patients, not only on the skin but also on serosal surfaces such as intestines; catastrophic cases of bowel perforation have been described. Therefore, special filters need to be applied to the lights in the operating room. Patients with EPP are also at risk for biliary complications, reported in 45%. Some experts recommend performing Roux-en-Y reconstruction for these patients.

> Because liver transplant does not correct the primary metabolic defect in patients with EPP, recurrent liver disease is diagnosed in more than 65% after the procedure.

While preparing for liver transplant, other interventions should be undertaken to rapidly decrease the levels of protoporphyrin. The assistance of colleagues in hematology is important because plasma exchange therapy or red blood cell exchange therapy is needed to quickly and significantly decrease the plasma level of protoporphyrin as well as to reduce exposure of the liver to protoporphyrins. Use of intravenous hemin, which is usually reserved for acute hepatic porphyrias, has been reported. Often, because of the severity of the situation, multiple interventions are recommended sequentially; for example, a patient might undergo plasma exchange followed by red blood cell exchange and then perhaps a session of intravenous hemin while waiting for liver transplant.

Because liver transplant does not correct the primary metabolic defect in patients with EPP, recurrent liver disease is diagnosed in more than 65% after the procedure. A curative therapeutic approach involves allogenic stem cell transplant. However, this is a high-risk procedure with high morbidity and mortality, so all of the risks and benefits need to be considered. Sequential liver transplant and hematopoietic stem cell transplant have been performed in a small number of patients to avoid recurrence in the liver allograft.

G&H Are there any drugs in development specifically for the treatment of EPP-associated liver disease?

CL Unfortunately, the short answer is no. Only one medication, afamelanotide (Scenesse, Clinuvel Pharmaceuticals), has been approved for the treatment of EPP. Afamelanotide is a melanocortin-stimulating hormone analog that induces the production of melanin. Patients are protected from sunlight because their skin becomes darker. However, this agent does not affect liver disease associated with EPP. Another drug in development with a similar mechanism of action is the melanocortin receptor agonist dersimelagon. This agent recently completed a phase 3 trial. However, it does not have the potential to alleviate or prevent liver dysfunction.

The glycine transporter inhibitor bitopertin is currently undergoing a phase 2 trial in patients who have EPP and XLP, and this agent has been shown to lower protoporphyrin levels in animal models. It is not currently being studied for its ability to prevent liver disease. However, if it significantly lowers plasma protoporphyrin levels, decreased hepatic exposure would be expected; thus, it may have potential to help in the management of liver disease.

Inhibition of the ABCG2 transporter seems like an attractive approach to potentially prevent the excretion of protoporphyrin in bile and mitigate hepatic injury, but therapeutic trials have not been initiated.

G&H Is there anything else that gastroenterologists and hepatologists should be aware of regarding EPP and liver involvement?

CL The level of awareness and general knowledge of porphyrias needs to be increased. Gastroenterologists and hepatologists are not very familiar with EPP, but it is important to know that EPP has the potential to cause significant liver damage despite being a cutaneous porphyria. To diagnose liver involvement earlier and to better understand the natural history of this disease, a lower threshold should be used to obtain liver biopsies in this population. Finally, it is also important to use a multidisciplinary treatment approach with colleagues from genetics, dermatology, and hematology.

G&H What are the most important next steps in research in this area?

CL Large collaborative studies that can evaluate the natural history of liver involvement in EPP are very important. Also important is new drug development to lower the levels of plasma protoporphyrin and decrease exposure of hepatocytes and cholangiocytes to this cytotoxic substance.

Disclosures

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Suggested Reading

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