Erythropoietic Protoporphyria (EPP) & X-Linked Porphyria (XLP)

OVERVIEW

EPP is the most common porphyria in children with an estimated prevalence of 1 in 75,000 to 1 in 200,000 in the European population. The prevalence in the US is not known. Most cases are caused by the markedly reduced activity (<30% of normal), of ferrochelatase, the last enzyme in the heme biosynthetic pathway which catalyzes the insertion of iron into protoporphyrin to form heme. Deficiency of ferrochelatase results in the accumulation of protoporphyrin which is highly photoactive leading to the clinical symptoms.

In 2-10% of cases, the clinical symptoms of EPP are caused by a gain of function mutation in erythroid specific δ-aminolevulinate synthase-2 (ALAS2) gene, which has X-linked inheritance. This is identified as X-linked Protoporphyria (XLP). As a result, the bone marrow produces more protoporphyrin than is needed for hemoglobin synthesis.

In both EPP and XLP, protoporphyrin accumulates in the marrow and is transported to the skin in the plasma and red blood cells, where it initiates a photosensitivity reaction when the skin is exposed to sunlight. Protoporphyrin is not excreted by the kidneys, but is taken up solely by the liver and excreted in bile. Clinical and experimental studies have shown that this can impair bile formation and cause hepatobiliary injury, a condition called protoporphyric hepatopathy.

SYMPTOMS

Photosensitivity begins in early childhood, and can be difficult to diagnose, since there is usually no skin blistering or physical findings on exam. Photosensitivity can present within minutes of exposure to sunlight with severe burning pain on the sun exposed areas of the skin (generally the dorsum of the hands, feet and face). These episodes of pain may last for days, and are usually unresponsive to any analgesics. The pain may be accompanied by localized swelling and erythema of the affected areas depending on the length of sunlight exposure. Patients are also sensitive to sunlight that passes through window glass (long wave ultraviolet light, or UVA). These symptoms greatly impair quality of life and limit employment opportunities and life style.

LONG TERM COMPLICATIONS

Large amounts of protoporphyrin in bile can cause a formation of gallstones rich in this porphyrin. Approximately 28% of patients have abnormal liver enzymes, and 1-5% have severe hepatobiliary injury from protoporphyrin toxicity that may necessitate liver transplantation. About 40% of patients have anemia which is usually mild and microcytic. They have features typical of iron deficiency, with low serum ferritins and transferrin saturations, even in the absence of apparent GI bleeding or other reasons for iron deficiency.

TREATMENT & PROGNOSIS

Systematic reviews and abundant patient accounts show that drugs such as β-carotene (Lumitene) or cysteine show no evidence of efficacy.

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TREATMENT & PROGNOSIS

Afamelanotide (Scenesse), an analogue of alpha-melanocyte stimulating hormone, administered as a subcutaneous biodegradable implant was FDA approved for the treatment of adults with EPP and XLP in 2019. MT-7117 is a novel orally administered melanocortin 1 receptor agonist, which is currently in Phase 3 clinical trials for EPP and XLP.

MANAGEMENT

Protoporphyric liver failure can appear suddenly and progress rapidly. Liver function tests should be done annually. A rise in serum aminotransferases, alkaline phosphatase, or total bilirubin, without other explanation should be evaluated by additional serological and other testing, by liver imaging, and/ or biopsy for evidence of protoporphyric hepatopathy or other forms of incident liver disease, such as viral hepatitis, auto-immune liver disease, drug-induced liver disease, or others. Because of the increased prevalence of gall stones at early ages in EPP/XLP, it is important to assess for these and for evidence of extra-hepatic biliary obstruction. If the latter is found, it is important to correct the disease as promptly as possible, in order to minimize cholestatic liver disease, which is a major risk in EPP/XLP.

If after careful evaluation, the cause of the liver disease is determined to be protoporphyric hepatopathy, the treatment regimen for this generally involves a combination of plasmapheresis, blood transfusion, intravenous hemin, cholestyramine, vitamin E, and ursodeoxycholic acid. Exchange transfusions, designed to remove RBCs loaded with protoporphyrin, have also been successful as part of management. Levels of porphyrins in plasma and red blood cells should be followed closely during treatment. Liver transplantation is sometimes necessary, but it remains difficult to predict which patients will develop liver failure. Bone marrow transplantation (BMT) is potentially curative in both EPP and XLP and will prevent recurrent damage to the transplanted liver. BMT without prior liver transplantation may also be considered in carefully selected patients with severe EPP/XLP and with PP hepatopathy that is pre-cirrhotic. One may anticipate that successful BMT will, over time, lead to marked decrease in PP load and to gradual improvement in PP liver disease. However, BMT does carry with it major risks of adverse effects, including acute or chronic graft-vs-host disease.

PREVENTION

Most patients learn to avoid sunlight as much as possible. Patients should be routinely screened for iron and vitamin D deficiencies and started on supplementation if clinically indicated. There is anecdotal evidence supporting improvement in severity of XLP with iron therapy. Iron supplementation may be considered for EPP patients who are symptomatic from iron deficiency and/or have hemoglobin levels <10 g/dL and a ferritin <10ug/L, with consideration of the individual patient's risk of worsened photosensitivity versus benefit from iron supplementation. To avoid preventable injuries to the liver, Hepatitis A and B vaccinations are recommended, as is the avoidance of excessive alcohol use and other potential hepatotoxins.

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FAMILY TESTING & COUNSEING

The inheritance of EPP is autosomal recessive. In about 90% of cases, a loss of function mutation in the (FECH) gene is inherited on one allele with a common low expression genetic variant IVS3-48C on the other. This common genetic variant is only disease causing in the presence of a pathogenic FECH mutation in trans. The frequency of this low expression allele in the FECH gene varies by population. It is present in about 43% of Japanese, 31% of Southeast Asians, 10% of Caucasians, and 1 to 3% of African Americans. Alternatively, about 5% of patients inherit two loss of function FECH mutations.

First-degree family members are generally carriers. The recurrence risk of EPP in children of an affected individual depends on whether the partner carriers a FECH mutation or, more likely, the low expression allele.

References

1. Wensink D, et al. Liver involvement in patients with EPP. 2021.
2. Balwani M. Erythropoietic Protoporphyria and X-Linked Protoporphyria: pathophysiology, genetics, clinical manifestations, and management. 2019.

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