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Review article

Erythropoietic Protoporphyria and X-Linked Protoporphyria: pathophysiology, genetics, clinical manifestations, and management

Manisha Balwani*

Department of Genetics and Genomic Sciences and Medicine, Icahn School of Medicine at Mount Sinai, New York, NY 10029, United States

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ABSTRACT

Erythropoietic Protoporphyria (EPP) and X-linked Protoporphyria (XLP) are rare, genetic photodermatoses resulting from defects in enzymes of the heme-biosynthetic pathway. EPP results from the partial deficiency of ferrochelatase, and XLP results from gain-of-function mutations in erythroid specific *ALAS2*. Both disorders result in the accumulation of erythrocyte protoporphyrin, which is released in the plasma and taken up by the liver and vascular endothelium. The accumulated protoporphyrin is activated by sunlight exposure, generating singlet oxygen radical reactions leading to tissue damage and excruciating pain. About 2–5% of patients develop clinically significant liver dysfunction due to protoporphyrin deposition in bile and/or hepatocytes which can advance to cholestatic liver failure requiring transplantation.

Clinically these patients present with acute, severe, non-blistering phototoxicity within minutes of sun-exposure. Anemia is seen in about 47% of patients and about 27% of patients will develop abnormal serum aminotransferases. The diagnosis of EPP and XLP is made by detection of markedly increased erythrocyte protoporphyrin levels with a predominance of metal-free protoporphyrin. Genetic testing by sequencing the *FECH* or *ALAS2* gene confirms the diagnosis.

Treatment is limited to sun-protection and there are no currently available FDA-approved therapies for these disorders. Afamelanotide, a synthetic analogue of α-melanocyte stimulating hormone was found to increase pain-free sun exposure and improve quality of life in adults with EPP. It has been approved for use in the European Union since 2014 and is not available in the U.S. In addition to the development of effective therapeutics, future studies are needed to establish the role of iron and the risks related to the development of hepatopathy in these patients.

1. Introduction

Erythropoietic Protoporphyria (EPP) and X-linked Protoporphyria (XLP) are rare, genetic photodermatoses resulting in acute, painful, photoxicity on sun-exposure [1]. EPP results from the deficient activity of ferrochelatase, the final enzyme in the heme-biosynthetic pathway [1] (Fig. 1). XLP, a less common condition, results from gain-of-function mutations in erythroid-specific aminolevulinic acid synthase (*ALAS2)* gene [2].

EPP is the most common porphyria in children, usually manifesting in infancy or early childhood after sun exposure with acute, painful photosensitivity [1]. The prevalence estimates of EPP range from 1:75,000 in the Netherlands to 1:200,000 in the United Kingdom [3,4]. XLP accounts for about 2% of cases in Europe and approximately 10% of cases in the United States [4,5].

2. Pathophysiology

The deficiency of FECH or gain-of-function mutations in ALAS2 both result in the accumulation of protoporphyrin IX (PPIX) [1,2,6]. FECH is responsible for the insertion of iron into PPIX to generate the final product heme. When FECH is deficient to < 30% enzyme activity, there is an increased accumulation of PPIX [1]. ALAS2 is highly expressed in erythroid tissues and provides a regulatory role in rate of erythroid heme biosynthesis. When this is disrupted in XLP, the rate of ALA formation is increased, and the insertion of iron into PPIX by FECH becomes rate-limiting for heme synthesis in erythroid tissues resulting in accumulation of protoporphyrin [2,6]. Protoporphyrin is released from the bone marrow into the circulating erythrocytes and plasma where it is taken up by the liver and vascular endothelium including the superficial skin vasculature. The protoporphyrin molecules are photodynamic and absorb light radiation in visible blue-violet light in the

* Corresponding author at: Department of Genetics and Genomic Sciences, One Gustave L. Levy Place, Box 1497, New York, NY 10029, United States.
E-mail address: manisha.balwani@mssm.edu.

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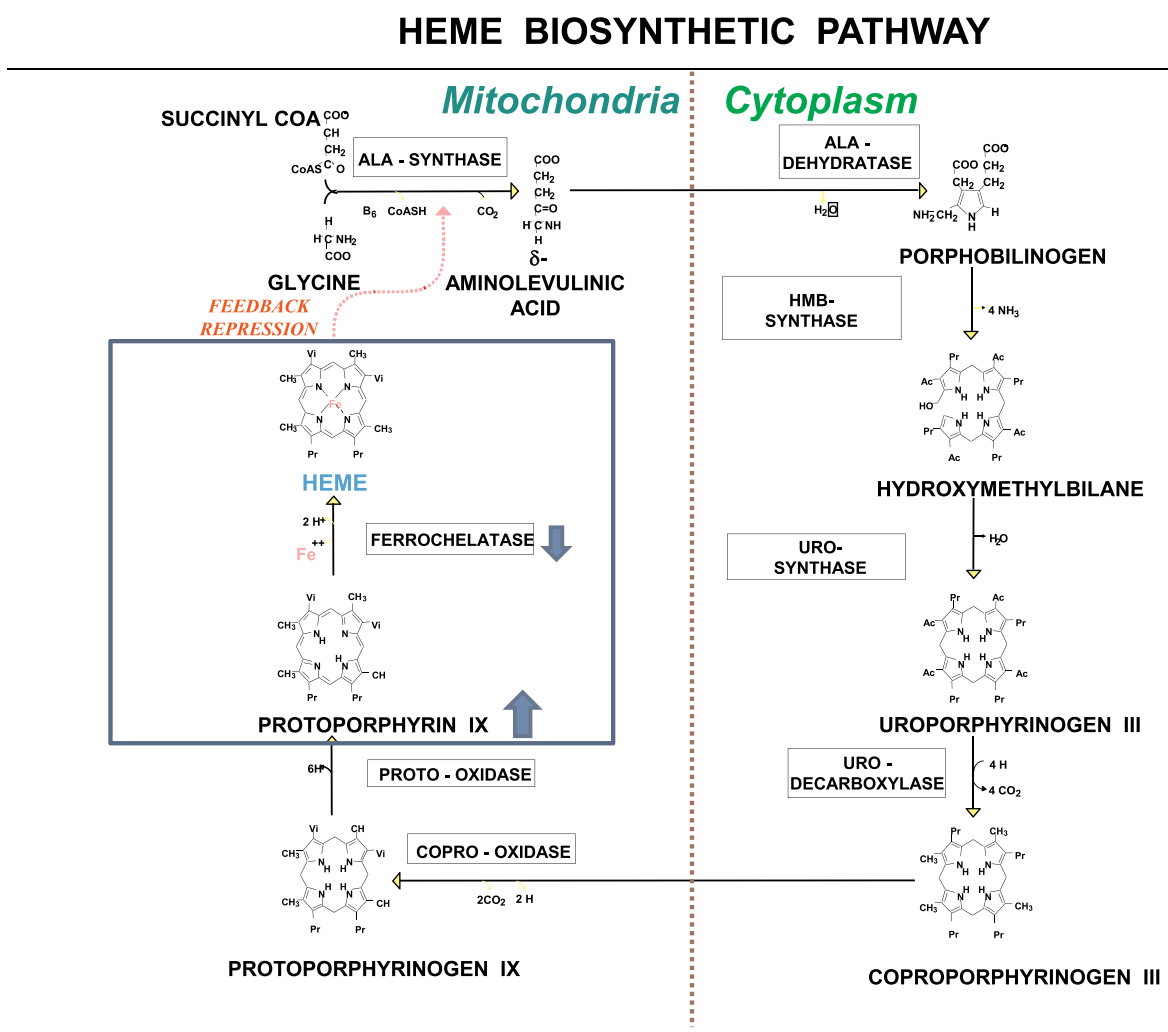

Fig. 1. Heme biosynthetic pathway.

Soret band and to a lesser degree in the long-wave UV region [7,8]. When porphyrins absorb light they enter an excited energy state. This energy is presumably released as fluorescence and by formation of singlet oxygen and other oxygen radicals that can produce tissue and vessel damage secondary to activation of the complement system. The release of histamines, kinins, and chemotactic factors may mediate skin damage [9]. Accumulated hepatic protoporphyrin can precipitate in hepatocytes and bile canaliculi, causing hepatotoxicity, decreased bile formation and flow, and cholestatic liver failure in some patients [10,11].

3. Genetics

EPP is autosomal recessive in inheritance [12]. Around 96% of patients with EPP have a loss of function *FECH* mutation *in trans* with a second low-expression pathogenic variant c.315-48 T > C (IVS3-48 T > C) [4,5]. The IVS3-48 T > C allele creates a cryptic upstream acceptor site in intron 3 that modulates the alternative splicing of the normal FECH mRNA, resulting in FECH activity < 30% of normal [13,14]. The prevalence of EPP may vary based on the allele frequency of the low-expression allele, which ranges from approximately 1%–3% in Africans, 10% in Caucasians to approximately 43% in the Japanese population [15]. Rarely patients can inherit bi-allelic loss-of-function mutations in *FECH*. This accounts for about 4% of cases in Europe [4].

Over 190 mutations have been reported in the *FECH* gene including, missense, nonsense, splicing and frameshift mutations [16]. EPP is 100% penetrant, males and females are equally affected [12]. Although the literature suggests that patients who are homozygous for the low expression allele are asymptomatic, a recent report from Japan identified three children homozygous for the common low expression IVS3-48 T > C allele who had slightly elevated free protoporphyrin levels and a mild presentation of EPP [17].

XLP results from gain-of-function mutations in erythroid-specific ALAS2 [2]. Mutations associated with XLP have only been observed in exon 11, which encodes the C-terminus, and result in a gain-of-function of ALAS2. These mutations result in stop or frameshift lesions that prematurely truncate or abnormally elongate the wild-type enzyme, leading to increased ALAS2 activity [2,5]. In XLP, all males are affected [18]. In heterozygous females with XLP, the random X-inactivation pattern directly influences the penetrance and the severity of the phenotype. XLP females can be asymptomatic clinically with normal protoporphyrins, be asymptomatic clinically with slightly elevated protoporphyrin levels or have significant symptoms based on the pattern of X-inactivation [18,19].

About 4–6% of patients with the symptoms of EPP and elevated erythrocyte protoporphyrin levels will not have mutations in *FECH* or *ALAS2* [4,20].

Recently, an autosomal dominant mutation in human CLPX, a modulator of heme biosynthesis, was found to result in the accumulation of protoporphyrin and symptoms of protoporphyria in an affected family [21]. Acquired somatic *FECH* mutations have been identified in a small number of patients in whom EPP has developed after the age of

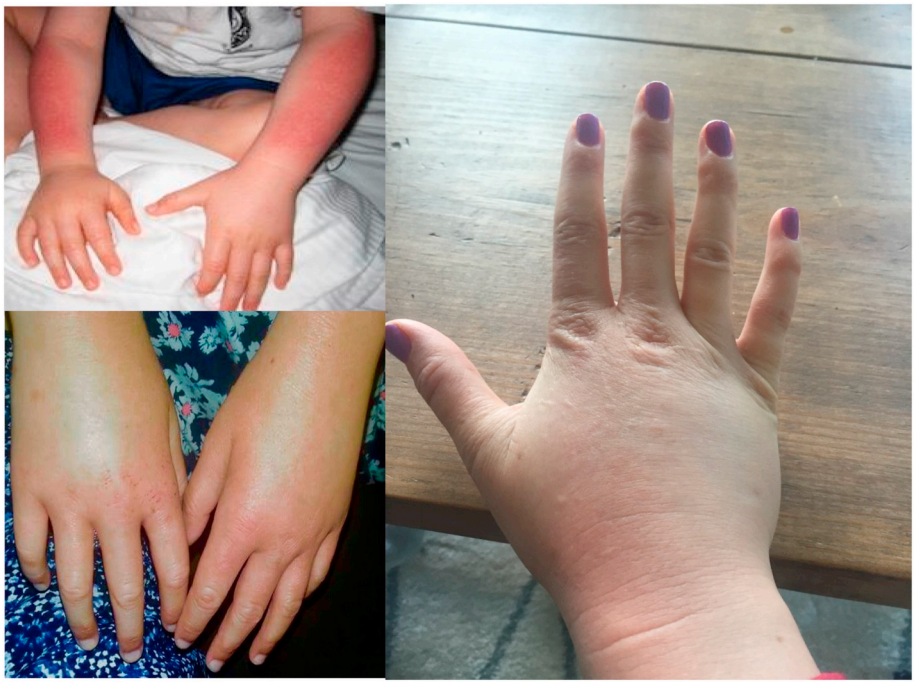

Fig. 2. Clinical manifestations: Erythema and edema on the dorsum of hands and forearm seen after acute phototoxic episode.

40 years in association with myelodysplasia or myeloproliferative disorder [22,23]. A case of late-onset EPP with myelodysplastic syndrome has also been reported in a patient who had the homozygous IVS3-48 T > C polymorphism in the *FECH* gene [24]. Late onset XLP has also been reported in a case of early myelodysplastic syndrome with somatic mosaicism in the bone marrow [25].

4. Clinical presentation

4.1. Cutaneous manifestations

EPP and XLP present with acute, painful phototoxicity on sun-exposure starting in infancy or childhood [1]. The mean age of symptom onset is about 4 years [20]. The pain is usually preceded by tingling, itching and burning sensation of the skin which may occur within minutes of sun exposure [9]. Patients can develop erythema and edema of the sun exposed skin [8] (Fig. 2). Vesicles or bullous lesions are uncommon in these disorders. Severe scarring, hypo or hyperpigmentation, skin friability and hirsutism are not typically seen [9,26]. Blistering was self-reported by about 26% of patients in one large series [20].

The dorsum of the hands and face are most commonly affected but any sun exposed area can be affected. Patients may be more sensitive to sun exposure the day after an acute phototoxic phenomenon [27]. With chronic sun-exposure, patients may develop lichenification and grooving around the lips [9]. Palmar keratoderma has been reported in some individuals with two loss-of-function *FECH* mutations [28].

EPP patients have significant clinical variability, with some patients who are unable to tolerate even a few minutes of sun exposure and others who can tolerate several hours [20]. Most patients develop symptoms within 30 min of sun exposure. The pain is severe and the symptoms may seem out of proportion to the skin lesions or lack thereof. The pain is not responsive to analgesics, including narcotic analgesics. Recovery from symptoms may take up to 4–7 days [20]. Symptoms may also vary based on environmental conditions including season, cloud cover, intensity and extent of sun-exposure and time of day [29]. With time, most patients are able to recognize the prodromal symptoms of EPP (e.g. itching and tingling) which serve as a warning sign to seek shade. Patients also develop a conditioned behavior of sun-avoidance which significantly impacts their daily activities.

4.2. Hepatobiliary disease

The excess protoporphyrin in EPP and XLP is excreted by the liver into the bile where it enters the enterohepatic circulation [30]. Progressive accumulation of protoporphyrin may occur in the liver when the biliary excretion does not keep pace with the load being presented to the liver. When hepatocellular damage reaches a critical stage, protoporphyrin accumulation will rapidly accelerate due to marked impairment of biliary excretion [11,12]. Concomitant conditions such as viral hepatitis, excessive alcohol consumption, and use of drugs which induce cholestasis may contribute to worsening liver disease. End-stage liver disease is typically preceded by an elevation in plasma and erythrocyte protoporphyrin levels. Patients may also develop a motor neuropathy in the setting of liver failure [31,32].

The excess amounts of free protoporphyrin may become insoluble and aggregate in the hepatocytes and small biliary radicals leading to obstruction to bile flow and cholestasis. About 20–30% of patients with EPP will have elevations in serum aminotransferases [20]. Protoporphyrin in bile may also crystallize forming gallstones. In one series, cholelithiasis were seen in 23.5% of patients [20].

4.3. Anemia

Mild anemia, typically microcytic anemia can be seen in EPP patients [33]. Patients with EPP appear to have an abnormal iron metabolism but the mechanism of iron deficiency is unclear [34,35]. The etiology of microcytic anemia and low iron and ferritin levels in EPP patients is unknown [36,37]. Previous studies suggest that EPP and XLP patients have normal iron absorption and an appropriate hepcidin response [38]. The iron deficiency in these disorders does not appear to be related to chronic inflammation or iron loss. The cause and mechanism of iron deficiency in these patients remains to be elucidated.

4.4. Vitamin D deficiency

EPP and XLP patients can develop vitamin D deficiency secondary to sun avoidance [39,40]. A recent report showed that the prevalence of osteopenia and osteoporosis is increased in patients in EPP [41].

5. Diagnosis

5.1. Biochemical testing

The biochemical diagnosis of EPP is established by the detection of significantly elevated total erythrocyte protoporphyrin with a predominance (85%–100%) of metal-free protoporphyrin [1,13]. Ferrochelatase can utilize metals other than iron and it catalyzes the conversion of the remainder of the protoporphyrin after hemoglobinization to zinc. As ferrochelatase is deficient in EPP, it limits the formation of both heme and zinc protoporphyrin [42]. In X-linked Protoporphyria, total erythrocyte protoporphyrin is also significantly increased with a lower fraction of metal-free protoporphyrin (50%–85% of the total) as ferrochelatase activity is normal in these patients [42].

It is important to distinguish metal-free protoporphyrin from zinc-chelated protoporphyrin on laboratory testing, as several other conditions such as lead poisoning, iron deficiency, anemia of chronic disease, and various hemolytic disorders may lead to elevation of erythrocyte protoporphyrin, usually zinc protoporphyrin [42]. Plasma total porphyrins are also increased in EPP and XLP. If plasma porphyrins are increased, the fluorescence emission spectrum of plasma porphyrins at neutral pH can be characteristic at 632–634 nm and can distinguish EPP and XLP from other porphyrias [42,43].

5.2. Genetic testing

The diagnosis of EPP is confirmed by identification of biallelic mutations by sequencing the *FECH* gene [44]. Gene targeted deletion/duplication analysis maybe useful if only one pathogenic variant is found [45]. In XLP, ALAS2 sequencing confirms the diagnosis [4,5].

There is limited information about genotype-phenotype correlation in EPP and XLP. Recent studies have shown that protoporphyrin levels were significantly lower in patients with EPP compared to XLP males [20]. EPP patients with a missense mutation in the *FECH* gene have lower protoporphyrin levels compared to patients with *FECH* deletions, nonsense or splice site mutations. The higher the level of erythrocyte protoporphyrin, the more likely that the patient will be more severely symptomatic characterized by decreased sun tolerance and increased risk of liver dysfunction [20]. In addition, some studies suggest that severe *FECH* mutations on both alleles may have an increased risk for severe liver disease [46–48].

6. Monitoring

Patients with EPP and XLP should have a comprehensive baseline evaluation on diagnosis and annual monitoring. The initial evaluation should include a comprehensive medical history including history of phototoxicity and a physical including thorough skin examination.

Baseline biochemical testing should include erythrocyte protoporphyrin including metal-free and zinc protoporphyrin levels. Plasma total porphyrins with the fluorescence spectrum can be helpful for confirming the diagnosis. All patients with an elevated protoporphyrin level with an excess of metal-free protoporphyrin should have genetic testing by sequencing the *FECH* and/or *ALAS2* gene as biochemical results may not reliably differentiate between EPP and XLP [20].

Additional laboratory testing should include a complete blood count to evaluate for anemia, and an iron profile including ferritin. Levels of vitamin D should be assessed to rule out any deficiency. Hepatic function panel including serum aminotransferases should be included to evaluate liver dysfunction. In patients with elevated liver enzymes, a more detailed work up is warranted to rule out other etiologies of liver dysfunction. Hepatic imaging with ultrasound is recommended if cholelithiasis is suspected. Newer diagnostic modalities such as Fibroscan may be helpful in assessing liver involvement in EPP and XLP, however, its utility has not been validated in these diseases. Liver biopsy may be indicated in some cases to evaluate for protoporphyric liver disease.

Patients with EPP and XLP should be recommended vaccination against hepatitis A and B to avoid preventable causes of liver injury. Vitamin D supplementation is recommended for patients who are deficient to avoid long term bone complications.

Patients and their families should be counseled about sun protection including the use of protective clothing. Annual follow up should be recommended and include laboratory studies including protoporphyrin levels.

Close monitoring is recommended for patients on iron therapy including complete blood count, iron indices and liver enzymes.

7. Management

7.1. Phototoxic reactions

Phototoxic reactions can be severe and do not respond to analgesics, including narcotic analgesics. Use of cold compresses or cold air on the sun exposed areas has been reported to help some patients. Oral corticosteroids and anti-histamines have been used to manage pain and swelling but the benefits are unclear.

7.2. Sun Protection

The mainstay of treatment for EPP is sun avoidance and/or sun protection. Most patients manage their disorder by modifying their lifestyle to limit sunlight exposure. Long sleeved clothing, gloves, wide brimmed hats and sun glasses can be used to minimize exposure to UV light. In addition, tinted windows can be used to prevent sun exposure while driving.

Topical sunscreens do not protect against phototoxic reactions as they are not formulated to protect against UVA and visible light. Sunscreens with opaque physical protective such as zinc oxide or titanium dioxide can provide some protection but may not cosmetically acceptable. A recent report showed benefits of a makeup base with photoprotective products designed for the protoporphyrin IX absorption spectrum in a small cohort of Japanese patients [49].

Phototherapy with gradual exposure to artificial ultraviolet lights has been used to induce increased light tolerance over time [50,51]. There have been no clinical trials to show an improvement in sun tolerance with phototherapy.

7.3. Drugs

Oral beta-carotene has been used to improve sun tolerance in patients. The dose depends on age and needs to be adjusted to maintain serum carotene at a level high enough to cause mild skin discoloration due to carotenemia [52,53]. Other drugs such as *n*-acetyl cysteine, cysteine and vitamin C have also been tried in EPP. However, there are no data to support the efficacy of these treatments in EPP [54]. High dose cimetidine has been reported to benefit pediatric patients with EPP but there is no clear clinical data or mechanistic evidence supporting this therapy [55,56].

Afamelanotide (Scenesse), a subcutaneously administered implant, is a potent analogue of the human α-melanocyte stimulating hormone (α-MSH). Afamelanotide binds to the melanocortin 1 receptor in dermal, increasing the production of eumelanin which is photoprotective [57]. The results of two multicenter, double-blind, placebo controlled, Phase 3 clinical trials in Europe and the U.S. showed an increase in pain free sun exposure in adult patients compared to controls. In the European study, there was a decreased number of

phototoxic reactions in the afamelanotide group. In both trials, there was an improvement in quality of life with afamelanotide [58]. In a long term observational study over 8 years, afamelanotide was shown to be safe and well tolerated, with good clinical effectiveness and an improvement in quality of life [59]. Scenesse has been approved for use for adults with EPP by the European Medicines agency in December 2014. It is currently pending evaluation by the U.S. Food and Drug Administration.

7.4. Liver disease

Hepatic complications can be seen in a small subset of EPP patients. In about 1–5% of patients, this may progressive to cholestatic liver failure requiring transplantation [11,30].

Liver transplant is the treatment for end-stage liver disease secondary to protoporphyrin related liver damage [31,60]. However, liver transplant is not curative as the primary source of protoporphyrin production is the bone marrow and liver transplant does not correct the underlying genetic defect [32]. Patients with EPP may develop a proximal motor neuropathy before or after liver transplant and require close monitoring. Bile acid sequestrants such as cholestyramine and other drugs such as ursodeoxycholelic acid have been used to increase the excretion of protoporphyrin through the biliary system [32,61]. Plasmapheresis, red cell exchange transfusion and intravenous hemin have also been used to decrease protoporphyrin levels before liver transplant although the effectiveness of these therapies has not been established [62,63].

EPP patients can develop skin and tissue burns during surgery for liver transplant due to activation of protoporphyrin by light in the blue-violet region. Use of special filters which block wavelengths below 470 nm is recommended during liver transplantation surgery [60].

There have been 62 liver transplants for pediatric and adult EPP patients reported [32]. *Re*-transplantation was needed in 7 cases. Post-transplant survival ranged from 47 to 66% at 10 year follow up [32].

7.5. Bone marrow transplant

Bone marrow transplant can be curative and sequential liver and bone marrow transplant has been successful in curing protoporphyric liver disease [64]. There have been several reports of pediatric patients receiving a bone marrow transplant following a liver transplant [65].

Wahlin et al. reported an adult with EPP who received a bone marrow transplant after medical management and reversal of cholestatic liver disease. A 2 year old with XLP and stage IV fibrosis also received a bone marrow transplant which stabilized liver disease [66]. Recently, a sequential liver and bone marrow transplant was reported in a 26 year old male with protoporphyric liver failure resulting in complete resolution of symptoms and normalization of protoporphyrin levels [67]. These reports suggest that in patients with liver disease who respond to medical management and have minimal fibrosis, bone marrow transplant may be performed without a need for liver transplant.

7.6. Iron supplementation in EPP and XLP

The role of iron metabolism in EPP and XLP is unclear. Microcytic anemia and low iron and ferritin levels can be seen in EPP patients, however, the etiology is unknown [36,37]. Previous studies suggest that EPP and XLP patients have normal iron absorption and an appropriate hepcidin response [38]. The iron deficiency in these disorders does not appear to be related to chronic inflammation or iron loss. The cause and mechanism of iron deficiency in these patients remains to be elucidated.

Clinical observations from previous case reports support that iron supplementation in XLP improves protoporphyrin levels and anemia and may help prevent progression of liver disease [68]. In EPP patients, iron therapy has been reported to both exacerbate and improve EPP symptoms [36,69]. These observations have been based on single case reports with limited monitoring and anecdotal reports of symptomatic improvement. Ongoing clinical trials looking at the role of iron in EPP and XLP may help with determining the effects of iron therapy in these patients.

8. Conclusions

EPP and XLP are rare photodermatoses with significant clinical heterogeneity. In addition to the development of effective therapeutics, future studies are needed to establish the risks related to the development of hepatopathy and the role of iron metabolism in these patients.

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