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Review Article

Erythropoietic Porphyria – Role of Curative Hematopoietic Stem Cell Transplantation

Devika Das[1], Ahmed Murad[2] and Ayman Saad[3]*

[1]*Division of Hematology and Oncology, University of Alabama at Birmingham, USA*
[2]*Department of Internal Medicine, Cairo University, Egypt*
[3]*Bone Marrow Transplant Program, University of Alabama at Birmingham, USA*

Corresponding author
Ayman Saad, Blood and Marrow Transplant Program, University of Alabama at Birmingham, 1720 2nd Avenue South NP 2560, Birmingham, AL 35294-3300, USA, Email: Asaad@uabmc.edu

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Abstract

Porphyrias are groups of heterogeneous metabolic disorders that result from derangement of the heme biosynthesis. There are 8 distinct subtypes each corresponds to a distinct enzymatic step in this pathway. There are generally classified as erythoid, hepatic and hepatic cutaneous disorders. Several mutations have been identified that result in these metabolic abnormalities. This group of disorders shares the fact that there is excessive heme biosynthesis intermediate, protoporphyrin that causes hepatic, cutaneous and neurological damage. Despite recent advancement in the diagnosis and mutation identification, no effective curative treatment is available for most of these disorders. Erythoid porphyria is likely an exception since hematopoietic stem cell transplantation (HSCT) has been used as a potential curative treatment. This report will highlight the pathogenesis of porphyrias and discusses the role of curative HSCT in erythroid porphyrias.

INTRODUCTION

The porphyrias are a group of metabolic disorders characterized by inherited defects in the heme biosynthetic pathway. Heme is an essential component of several hemoprotein such as hemoglobin, cytochrome enzymes and myoglobin. Heme is synthesized by incorporating iron into protoporphyrin IX ring in the mitochondira, a step catalyzed by the ferrochelatase enzyme. Hemoglobin synthesis in erythroid precursor cells accounts for about 85% of heme synthesis, while synthesis of cytochrome P450 enzymes in hepatocytes accounts for most of the other heme synthesis [1].

Heme biosynthesis involves 8 enzymatic steps that starts and ends in the mitochondria with intermediate steps taking place in the cytosol (Figure 1). The first step in heme biosynthesis is the synthesis of aminolevulonic acid (= ALA) from glycine and succinyl CoA under the enzymatic effect of ALA synthase [1]. These 8 enzymes are encoded by 9 genes as the first enzyme (ALA synthase) is encoded by 2 different genes; a housekeeping gene located on chromosome 3 (ALAS1 isoenzyme) and an erythroid-specific gene located on X chromosome (ALAS2 isoenzyme).

PATHOGENESIS AND CLINICAL PICTURE

The 8 types of porphyrias can be categorized into "erythroid", "hepatic" and "cutaneous hepatic" classes (Table 1). Each of the 8 types corresponds to a specific enzymatic deficiency in the heme biosynthesis pathway (Figure 1). The enzymatic defects of heme synthetic pathway result in pathological buildup of protoporphyrins. In case of erythoid porphyrias, the excess protoporphyrin is formed in the erythoid cells (in the bone

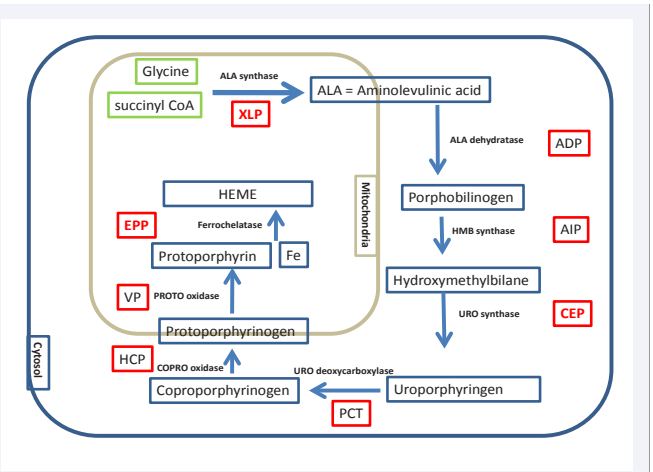

Figure 1 Heme biosynthesis pathway with different types of porphyrias shown in relation to their corresponding enzymatic defect.

ADP: ALA-dehydratase-deficient porphyria; AIP: acute intermittent porphyria; CEP: congenital erythropoietic porphyria; EPP: Erythropoietic porphyria; HCP: Hereditary coproporphyria; PCT: Porphyria cutanea tarda; VP: variegate porphyria; XLP: X-linked porphyria

Table 1: Clinical types of porphyrias.

Erythroid porphyrias
- CEP: Congenital erythropoietic porphyria
- EPP: Erythropoietic porphyria
- XLP: X-linked porphyria

Hepatic porphyrias
- ADP: ALA-dehydratase-deficient porphyria
- AIP: Acute intermittent porphyria
- HCP: Hereditary coproporphyria
- VP: Variegate porphyria

Hepatic cutaneous
- PCT: Porphyria cutanea tarda

marrow) and is released into the plasma where is it is taken up by the liver to be excreted in bile and feces. Since protoporphyrin is insoluble, it can result in formation of crystalline materials in the hepatobiliary system with cholestatic liver injury [3,4]. The transit of excessive protoporphyrin is the cutaneous blood vessels results in photoactivation by sun/light with subsequent blistering and scarring lesions. The excess protoporphyrin can also cause neuro-toxicity with neuropathic visceral (abdominal) pains and mental status change [1].

ERYTHROID PORPHYRIA

There are 3 distinct types of erythoid porphyria, CEP (congenital erythropoietic porphyria), EPP (erythropoietic porphyria), XLP (X-linked erythropoietic porphyria) (Table 1).

- EPP occurs due to ferrochelatase deficiency (autosomal dominant mutations) resulting in accumulation of free protoporphyrin resulting in painful blistering skin lesion and cholestatic liver injury. Molecular analysis has identified a variety of mutations associated with reduction of the ferrochelatase production [5].
- XLP occurs due to "gain-of-function" mutation of the ALAS2 (X-linked erythoid-specific gene) that results in excessive buildup of protoporphyrin [1]. The clinical picture of this disorder is similar to EPP. It is worth noting that "loss-of-function" mutation of ALAS2 (erythroid gene) results in a different bone marrow failure syndrome; X-linked sideroblastic anemia [6].
- CEP (also called Gunther disease) occurs due to deficiency of URO (uroporphyrin) synthase (autosomal recessive). Several mutations have also been identified in association with this deficiency. Patients typically present in early life and develop scarring skin lesions and severe liver damage.

Hepatic porphyrias

The commonest hepatic porphyria is AIP (acute intermittent porphyria), while ADP is rare. These disorders can present with severe and even life-threatening acute attacks characterized by neuro-psychological manifestation (seizure, neuropathy and altered mental status), acute abdominal pain and cutaneous manifestations [1]. Hereditary coproporphyria (HCP) and variegate porphyria are other autosomal dominant hepatic types with similar manifestations [7,8].

Hepatic cutaneous porphyria

Porphyria cutanea tarda (PCT) is the most common of all porphyrias. It can manifest as a sporadic or familial disease which is autosomal dominant with incomplete penetrance [9,10]. The disease is characterized by extreme photosensitivity and skin fragility with bullae formation and subsequent scarring and disfigurement of sun-exposed areas.

Treatment approaches

Common treatment approaches are summarized in (Table 2). Supportive care and prevention of attacks is the main treatment strategy for porphyrias. Acute attacks often present a clinical challenge as they can be life-threatening.

ROLE OF HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

HSCT has been used a curative treatment for erythroid porphyria. Replacement of erythroid hematopoietic tissue results in abrogation of the pathological buildup of protoporphyrin and sometimes resolution of organ damage induced by prior accumulation. There is no systematic study reported using HSCT in treatment of erythoid porphyria, however, plenty of case series have been reported.

An erythroid porphyria murine model study demonstrated that neonatal bone marrow transplantation can prevent liver disease and results in recovery of other porphyria-related manifestations [11].

In CEP (URO synthase deficiency), several reports of successful use of HSCT have been reported since early 1990s [12-17]. Volunteer unrelated donors have also been successfully used due to lack of available matched related ones. For example, HLA-matched unrelated donor bone marrow transplantation was used in 2 cases (a 4-year-old boy and his 4-year-old female cousin), who were born with CEP. They received myeloablative preparative regimen of busulfan/cyclophosphamide with thymoglobulin (ATG) prior to transplant. Both patients were alive at 3 years and one of them developed veno-occlusive disease (VOD) during the HSCT. Cutaneous lesions improved dramatically after HSCT [18]. A recent report also showed a 7-month-old boy to be alive 1 year after HSCT with clinical improvement of porphyria manifestation [19].

Table 2: Summary of treatment approaches of porphyrias.

Acute attacks
- Intravenous hemin and carbohydrate loading (300 gm glucose per day).
- RBCs transfusion: to suppress heme synthesis pathway.
- Plasmapheresis (can also be used periodically after liver transplant to prevent recurrence)

Long-term treatment
- Avoiding sunlight exposure and wearing protective clothing.
- Oral carotene (120-180 mg/dL), which causes a mild skin discoloration because of carotenemia, may improve tolerance to sunlight.
- Melanocyte-stimulating hormone analog that darkens the skin (increase tolerance to sunlight exposure)
- Cholestyramine and charcoal →absorb porphyrin in the gut → interrupt the enterohepatic circulation of protoporphyrin.
- Liver transplantation; recurrence is common in the transplanted liver.

Curative treatment
- HSCT can prevent liver damage and potentially cure porphyrias.

In patients with EPP (ferrochelatase deficiency), hepatocytes may be contributing to excess protoporphyrins [20]. Thus there has been reluctance to use HSCT to treat these patients. Instead, liver transplantation has been used for patients who develop severe liver damage [21]. However, attention to the role of HSCT as a curative treatment for EPP was noted after an interesting observation in a patient who underwent HSCT (bone marrow) for acute myeloid leukemia and also had EPP. After transplant, the patient was noted to have resolution of the EPP phenotypic manifestation (including skin photosensitivity) acquiring her brother (donor) genotype of single allele ferrochelatase mutation (autosomal recessive disease) [22]. This observation reported in 2002 obviously triggered interest in using HSCT as a potential cure for these patients. An example is reported successful HSCT done for a 62-year-old male. This patient rejected the first graft after a non-myeloablative regimen of fludarabine/Cytoxan/ATG regimen, but attained full donor chimerism after a second transplant using fludarabine/Cytoxan/TBI 6 Gy/ATG [23].

HSCT was also successfully used to treat patient with EPP after liver transplant [24]. A reported case showed salvaged by HSCT after recurrence of cholestatic liver injury following liver transplant. This patient initially underwent HSCT (after myeloablative cytoxan/total body irradiation), however, engraftment was only successful after splenectomy and a second HSCT using attenuated regimen busulfan/fludarabine/cytoxan with ATG regimen.

The favorable outcome of HSCT reported in patients with EPP suggests that replacement of erythoid tissue can circumvent the disease progression even with continued hepatic ferrochelatase deficiency.

There is no reported cases for the use of HSCT in XLP (ALAS2 gain-of-function mutation), a disorder that has only been recently identified. However, these patients may attain similar benefit compared to EPP.

CONCLUSION

It is reasonable to consider the use of HSCT in patients with erythroid porphyria (all three subtypes; CEP, EPP, and XLP) before significant liver damage occurs. Given the aggressive nature of CEP, transplant is often indicated during childhood. EPP, and in particular XLP, may have indolent course. Disease may first manifest in adulthood. Transplant is typically considered in eligible patients when they develop symptomatic disease particularly with hepatic involvement. Untreated cases may succumb to chronic liver disease and cirrhosis. Severe liver damage would preclude HSCT, in which case liver transplant can to be done at first followed by HSCT [24]. Allogeneic HSCT carries risk of treatment-related mortality that averages 14-40% depending on pre-transplant morbidities [25]. Several of the reported cases used myeloablative regimens; however, the use of reduced intensity or non-myeloablative regimens (fludarabine-based regimen) may offer a safer approach particularly in patients with hepatic impairment. The achievement of mixed chimerism may abolish the phenotypic manifestation of the disease, albeit risk of delayed graft rejection.

The Examples of reduced intensity regimen would be fludarabine/busulfan or fludarabine/melphalan regimens. This would be similar the use of these regimens in non-neoplastic benign blood diseases, such as HLH (hemophagocytic lymphohistiocytosis) [26-28]. The use of reduced intensity regimen of fludarabine/melphalan/alemtuzumab in HLH has improved the survival of these patients compared to the full intensity regimen [28]. Despite the risk of engraftment failure (early and delayed), the use of reduced intensity regimen has been associated with decreased transplant-related mortality and hence improved overall survival seems a reasonable justification for using this approach. Worsening chimerism following reduced intensity transplant can be salvaged by donor lymphocyte infusion as specifically shown in HLH [28].

There is an ongoing clinical trial using the reduced intensity regimen of fludarabine/melphalan/alemtuzumab as a conditioning regimen for sickle cell disease (*BMT CTN #0601*) registered on www.clinicaltrials.gov as *NCT00745420.* However, it is noted that the cord blood transplant cohort in this trial was closed due to high rate of graft rejection despite excellent overall survival [29].

The use of bone marrow rather than peripheral stem cell (PBSC) graft may be also appropriate to minimize risk of graft versus host disease (GVHD). However, patients who have received repeated blood transfusion may develop anti-HLA antibodies that impose high risk of graft rejection in particular with bone marrow graft. PBSC is generally more secure source of stem cells with least risk of graft rejection. It is recommended that GVHD prophylaxis regimen follow the standard approach with goal of stopping immunosuppression completely by 6 months in patients who do not develop GVHD. The use of haplo-identical or cord blood transplant may also be considered in eligible patients. There is no systematic data to support this approach, hence caution to be exercised. It is strongly recommended that these types of transplants be done in the context of clinical trial if possible.

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