Section A -Research paper

UNDERSTANDING ERYTHROPOIETIC PROTOPORPHYRIA(EPP) IS ESSENTIAL IN AN INDIAN CONTEXT. A PROSPECTIVE REVIEW.

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ABSTRACT

In people with EPP, a genetic porphyrin metabolism disorder, protoporphyrin levels are high in RBC, plasma, and feces. The disease appears in infants with varied photosensitivity. There is no animal model where high erythroid protoporphyrin levels may be produced under controlled circumstances to imitate human disease. EPP is a biochemically separate porphyrin and heme production disease. Patients acquire extreme, immediate photosensitivity to sunlight and other intense visible light. Gallstones often affect young people. Studies proved that liver disease, which may lead to pigmentary cirrhosis and liver transplantation, affects 1–3% of people. This is due to the fact that excess PP, which may be hepatotoxic, is eliminated through hepatocyte absorption and bile excretion. Since PP overproduction is largely due to red blood cell production, bone marrow or stem cell transplantation is needed to cure the disease. More longitudinal researches are needed in future.

Keywords: EPP**,** RBC**,** Gallstones**,** heme production disease & porphyrin.

INTRODUCTION

Studies have proved that ,EPP is a genetic porphyrin metabolism disorder resulting in elevation of PP levels in RBC, plasma and feces. Further, there is no increase in urinary porphyrin levels in EPP. Clinically, the disease is characterized by variable-severity photosensitivity that manifests in early infancy. It is not known what causes this condition.

Unfortunately, no animal model exists in which elevated erythroid protoporphyrin levels can be produced in a controlled setting to mirror the disease seen in humans.[1] Disease was presented by Kosenow and Treibs in 1953.[2] The disorder called as EPP was officially defined & named by Magnus et al. in 1961, with clear identification of its clinical and laboratory abnormalities.[3] Around 300 instances have been documented till now, from United States, Europe, India, Australia, and Africa.[4]

MECHANISM

Various studies have shown that, porphyrins are a family of compounds with a similar structure. They includes four types of pyrrole rings which are joined together by methene bridges. Here, 8 hydrogen atoms in the pyrrole rings are replaced by side chains, which vary in structure. They are either intermediates or oxidation products of intermediaries in the conversion of glycine & succinate to produce heme. In addition , porphyrinogens are nonfluorescent & colorless, while porphyrins are colorful compounds that fluoresce when exposed to light in the long ultraviolet spectrum's Soret Band (400–410 nm). Absorbed light energy may be dispersed in a variety of ways, including fluorescence & formation of free radicals and peroxides. Here, requisite enzymes and substrates for the biosynthesis of heme are present within hepatocytes, bone marrow, and numerous other tissues. Perturbations in the metabolic pathways of porphyrin may manifest in any of the aforementioned tissues. Porphyrias are typically categorized as either hepatic or erythropoietic based on the tissue that is believed to be impaired in porphyrin metabolism. EPP is characterized by a metabolic anomaly that leads to an overproduction of protoporphyrin IX. This compound is present in abnormally high concentrations in various tissues and fluids.[1]

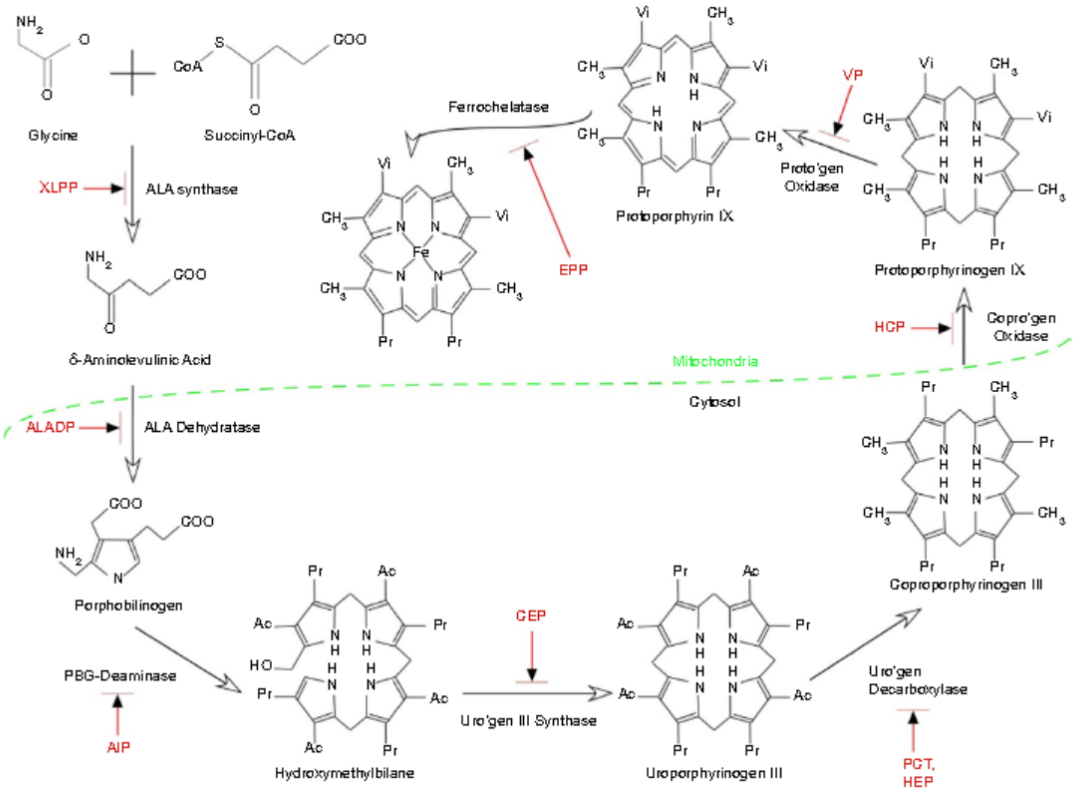

FIGURE 1: HEME SYNTHESIS[5]

Henceforth, initial assumption regarding the defect in question was that it was erythropoietic due to the heightened levels of RBC- PP observed in the disease.[3] The initial concept has been called into question by a number of researchers due to a range of clinical observations and experimental findings. The study conducted by Cripps and MacEachern revealed that the concentration of PP in the feces of the subjects diagnosed with EPP was not associated with the levels of RBC. The researchers postulated that the quantity of PP eliminated in the feces of these individuals exceeded the expected levels resulting from the typical mechanism of E degradation and subsequent release of surplus PP.[6] Further studies have utilized isotopically labeled glycine and aminolevulinic acid in patients diagnosed with EPP. However, the results of these studies have been inconsistent.[1]

While , if erythropoietic cells are excess then PP escapes in bile as breakdown products or unchanged form. Piomelli and his colleagues[7] showed in their study that leak occur in erythropoietic red cell protoporphyria, but Redeker et al.[8] were unable to demonstrate it.

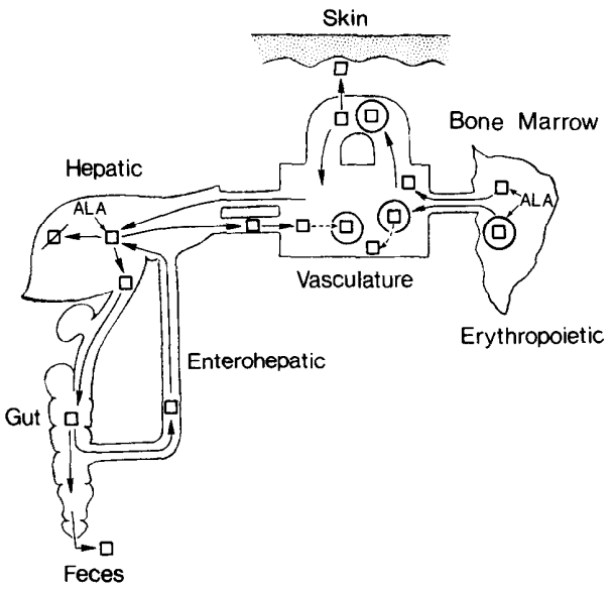

FIGURE 2: RELATION BETWEEN POSSIBE ORIGIN OF EXCESS PROTOPHYRIN IN EPP.[1]

EPIDEMIOLOGY & CLINICAL PRESENTATION

According to Various studies, EPP has been considered second most prevalent form of prophyria. There was no gender predominance across ethnic & racial groups for EPP. Studies have demonstrated that ,mostly affected patients were of early childhood with sensitivity to sun. In this infants & children classically develop brief exposure in spring & summer. Some studies have also shown that several hours later erythema, edema & itching become prominant.[9] Further , studies concluded that , if there will be chronic & repeated exposure of the involved skin , it could lead to leathery & hyperkeratotic skin.[9] Here, photoactiavtion of circulating water-soluble uroporphyrin leads to chronic blistering . According to various studies, development of pigmentary cirrhosis of liver leads to most serious complication of EPP.[10,11] However, no risk factors have been identified till date, that will be able to predict development of liver disease in EPP.[9] Researchers have also concluded ,common complication of EPP i.e. development of pigment gallstones (high content of PP). In addition, abdominal pain , neuropathy like symptoms may also seen sometimes.[12-15]

LABORATORY FINDINGS [9]

1. Increase level of PP, without increased level of coproporphyrin in stool & RBC.
2. Elevated level of EPP, plasma PP & stool PP
3. Urine porphyrin levels are normal usulaly as because PP is not excreted in urine .

4. Plasma prophryrin emission spectrum upto 634-636 nm following exciation with light in soret band upto 400 nm.
5. Do not have iron , lead toxicity

MANAGEMENT[9,5]

According to various studies ,a lot of treatment options are available for EPP ranging from reduce PP over production in bone marrow to augment its excretion into bile.

1. Ony tropical sunscreen is recommended (effective at blocking wavelength greater than 400 nm,with high sun protection factor (>30) , light opaque which contain zinc oxide or titanium dioxide).
2. Beta-carotene treatment (reduces photosensitivity in approximately 80%) .
3. Oral cysteine have found almost same results as that of beta- carotene.
4. Bile acid binding agents like cholestyramine can be used to decrease enterohepatic circulation of PP .
5. Intravenous Vitamin E (shown effective in many studies).
6. Ursodeoxycholic acid for early liver disease.
7. Patients should be under caloric restriction
8. Iron replacement (only if found iron deficient).
9. Advice for immunization i.e. HAV/HBV
10. Limit alochol intake (men : 2 drinks/ day) & women : 1 drink/day)
11. Illicit drug consumption or supplements .
12. Vitamin D3 therapy is advice.
13. Regular assessment of liver & gallbladder function.
14. Plasmapheresis, RBC exchange , intravenous heme therapy is adviced for acute hepatic decompensation.
15. Patient with severe disease & hepatic decompensation may required bone marrow transplantation & /or liver transplantation.

CONCLUSION

We conclude that, EPP is a biochemically separate and very unusual disease of porphyrin and heme synthesis. Patients exhibit acute and virtually immediate photosensitivity when exposed to sunlight or other intense visible light. Young people often get symptomatic gallstones. Studies have shown that, patients who develop liver disease, may leads to pigmentary cirrhosis and require liver transplantation. This is because excess PP is potentially

hepatotoxic and is removed from the body through hepatocyte uptake and bile excretion. Because the formation of red blood cells is the primary source of PP overproduction, bone marrow or stem cell transplantation is required to treat the disease. More longitudinal investigations are needed to validate the conclusions of our research.

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