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REVIEW ARTICLE **OPEN ACCESS**

A Brief Review on Erythropoietic Protoporphyria

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ABSTRACT

Studies show that EPP is a rare disease that builds up protoporphyrins in red blood cells. This can lead to severe photosensitivity, unbearable pain, and maybe even liver disease. Studies also concluded that the symptoms typically begin in early infancy and include sudden pain and sobbing when the youngster is exposed to intense sunshine. Researchers also found that one of the most noticeable signs of CEP is bullous skin that is sensitive to visible light from early childhood onward. Hence, according to various studies, progressive photomutilation and chronic hemolytic anemia are two other hallmarks of this condition. Thus, in our review, we were discussing EPP in terms of pathophysiology, signs and symptoms, genetic changes, biochemical, histological changes, D/D, prognosis, complication aspects and managment.

Key words: *EPP, pathophysiology, signs and symptoms, genetic changes, biochemical, histological changes, D/D, prognosis, complication aspects, management.*

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INTRODUCTION

Researchers have found that "erythropoietic protoporphyria (EPP), is a genetic disorder that causes too many protoporphyrins to build up in red blood cells".[1] Furthermore, studies have concluded that this results in acute photosensitivity that does not result in blistering and might potentially lead to liver damage. [1] Studies have also concluded that the symptoms typically begin in early infancy and include sudden discomfort and sobbing when exposed to intense sunshine. Additionally, studies have also concluded that it has a seasonal pattern, with symptoms manifesting themselves mostly in the spring and summer months of the year. Furthermore, studies have concluded that "EPP is a lifelong condition, and repeated phototoxic responses ultimately lead to thickening of the skin and wax-like scarring on the face".[2] Studies have concluded that this may occur in patients who have had EPP for a long time. In addition to this, studies have also concluded that the "accumulation of protoporphyrins in the liver may result in cirrhosis and liver failure in certain people".[2] However, this condition only affects a tiny percentage of patients. Hence, studies have concluded that there are very few cases in which the disease begins in adulthood; nevertheless, an acquired variant has been described. Studies have found that clones of cells with a mutant ferrochelatase gene grow in people with myelodysplastic or myeloproliferative syndrome.[2] Researchers have found that "congenital (C) EPP is also known as 'Gunther's illness,' after the physician who recognized it as an inborn metabolic defect and offered the first significant categorization of porphyrias by splitting them into acute and chronic types".[3] Studies have also concluded that C-EPP has been classified as chronic porphyria and is an exceptionally rare condition, with an estimated frequency of one in a million.[4] Studies have also proved with references that although this disease is of rare type yet around 300 instances have been documented about the same from around the world which includes US, Europe, India, Australia and Africa.[5] Thus, in our review we were discussing about EPP.

PATHOPHYSIOLOG

Several studies have concluded that "heme biosynthesis involves eight enzymes and a series of sequential reactions. The first enzyme in the process, d-aminolevulinate synthase (ALAS), is the rate-limiting step in hemolysis production. ALAS1 isoenzyme undergoes feedback inhibition by haem in hepatocytes. Iron and hemoglobin homeostasis are tightly connected to ALAS2 regulation in erythropoietic cells".[6] as shown in Figure 1

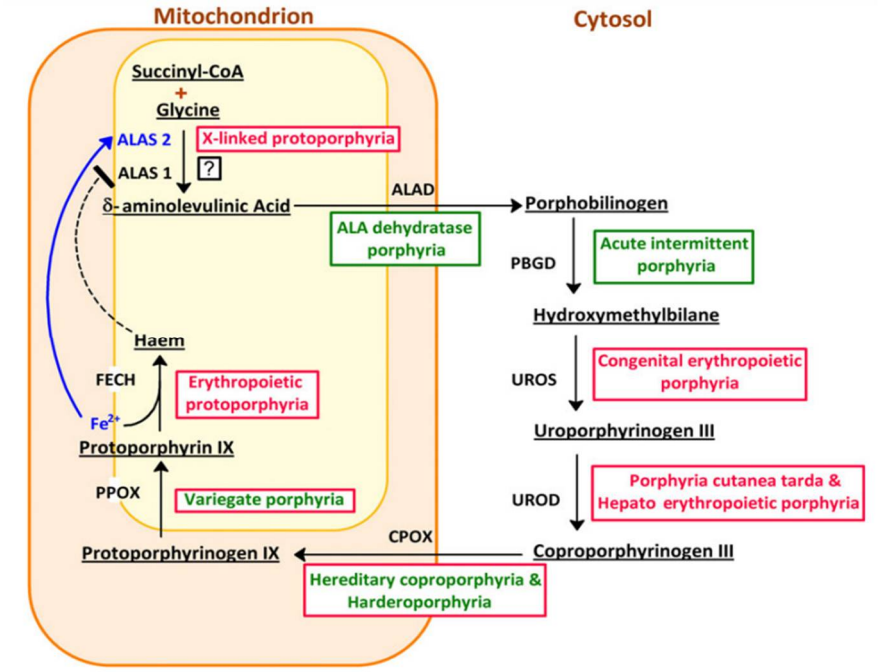

Fig. 1 : Several studies have concluded that "humans have porphyrias and enzymatic deficiencies. Every type of porphyria is caused by a unique deficiency in an enzyme. The porphyrias that are highlighted in green are known for their prominent neurological and acute symptoms. The porphyrias that are highlighted in red are characterized by chronic cutaneous photosensitivity. Both variegate, hereditary coproporphyria, and harderocoproporphyria exhibit symptoms that affect both the nervous system and the skin. Haem downregulates the ALAS1 gene in hepatocytes. The regulation of the ALAS2 gene in erythropoietic cells is intricately linked to the maintenance of iron and hemoglobin homeostasis. ALAS, d-Aminolevulinate synthase; ALAD, aminolevulinate dehydratase; PBGD, porphobilinogen deaminase; UROS, uroporphyrinogen III synthase; UROD, uroporphyrinogen decarboxylase; CPOX, coproporphyrinogen oxidase; PPOX, protoporphyrinogen oxidase; FECH, ferrochelatase".[4]

A number of studies have found that "UROS is the fourth enzyme in the pathway for making hemoglobin. It changes the shape and ring structure of the linear hydroxymethylbilane (HMB) to make uroporphyrinogen III. Some of the hydroxymethylbilane doesn't get changed by UROS, so it changes into the uroporphyrinogen - I isomer without the help of enzymes.[7] Although studies have concluded that uroporphyrinogen - I can be decarboxylated by UROD to form hepta-, hexa-, and pentacarboxyl porphyrinogen - I and, finally, coproporphyrinogen I, further metabolism is halted because the next enzyme in the pathway, coproporphyrinogen oxidase (CPOX), is stereospecific for the III isomer".[8] Figure 2.

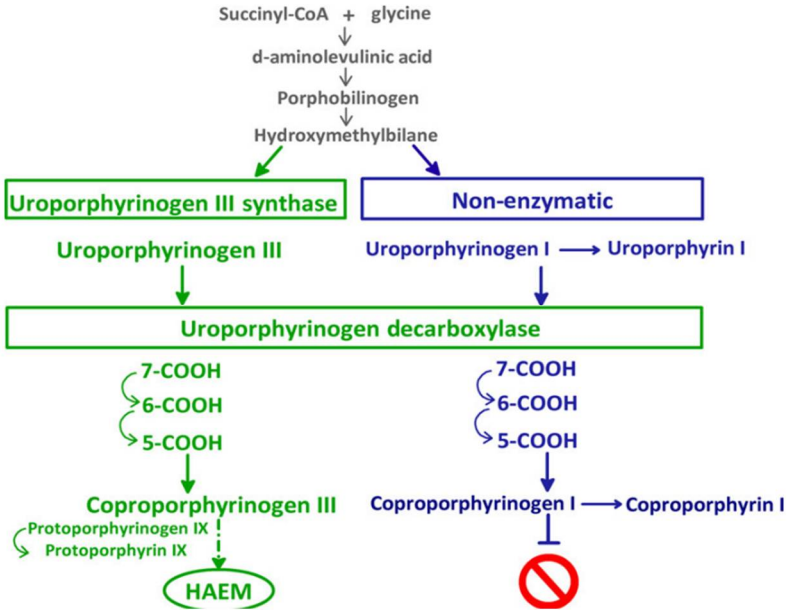

Fig. 2: This is the process of haem biosynthesis. The pathway is illustrated by green arrows, showcasing the physiological enzymes and intermediates, starting with hydroxymethylbilane. The non-enzymatic conversion to uroporphyrinogen I is indicated by the blue arrows. The enzyme uroporphyrinogen decarboxylase is responsible for converting both forms of uroporphyrinogen into coproporphyrinogen, which then undergoes further decarboxylation to produce the intermediates known as heptacarboxylporphyrin, hexacarboxylporphyrin, and pentacarboxylporphyrin. The next enzyme, coproporphyrinogen oxidase, only acts on isomer III, so coproporphyrinogen I does not undergo further catalysis.[4]

SIGN & SYMPTOM [9,10,11,12,13]

1. "Severe Haemolytic Anaemia
2. Mild Cutaneous Photosensitivitiy
3. Myleodysplasia
4. Thrombocytopenia
5. Neonatal Jaundice
6. Transfusion dependent Haemolytic Anaemia
7. Splenomegaly
8. Subepidermal Blistering
9. Hyperorthokeratosis
10. Flattening of dermoepidermal junction
11. Diffuse sclerosis in dermis
12. Total disappearance of sweat & sebaceous gland
13. Thick vascular wall
14. Thick hyalin deposit
15. Elastic fibre fragmentation
16. Hypopigmentation
17. Hyperpigmentation
18. Hypertrichosis
19. Extensive ulceration
20. Erosion
21. Scarring
22. Scarring alopecia
23. Malignant skin cells"

GENETIC CHANGES [4]

1. UROS Mutation
2. GATA1 Mutation
3. ALAS2 Mutation

GENETIC COUNSELLING

Many research studies have also shown that in the most common type of EPP, where there is an FECH mutation on one allele and a hypomorphic FECH IVS3-48C allele in the trans position, there is a less than 1% chance that the child of an EPP patient will also have the disease. This is also known as 2.5%. Studies have concluded that this type of EPP occurs when there is an FECH mutation on one allele and a hypomorphic FECH IVS3-48C allele in the trans position. This is because there is an FECH mutation on one allele and another allele, FECH IVS3-48C, that is hypomorphic and located in the trans location. According to studies, the hypomorphic FECH allele is found in about 10 to 20% of the Caucasians who live in the general population.[14,15] Researchers have found that a more accurate estimate of the chance that a person will develop EPP can be made by testing them to see if they have the FECH IVS3-48C hypomorphic allele. This screening is performed on the spouse of an EPP patient. In the great majority of cases, EPP does not put the health of the mother or the fetus at risk during pregnancy. The reported occurrences of pregnancy in patients with EPP have shown that symptoms of photosensitivity improve during pregnancy, with a drop in erythrocyte protoprophyrin levels.[16] Furthermore, studies have concluded that the only exception to this is a case that was only recently published. A case that was only recently reported is the only exception to this conclusion. To the above conclusion, there is only one potential exception, and that is this one.[16]

BIOCHEMICAL & HAEMATOLOGICAL ALTERATION

Several studies have also shown that a partial lack of FECH can lead to an increase in free protoporphyrin IX. In addition, studies have also shown that RBCs in circulation, bone marrow erythroblasts, and reticulocytes may all be detected. Furthermore, studies have also found that RBC will, as a consequence,

exhibit fluorescent properties when exposed to Wood's light. The plasma of patients may also have protoporphyrin detected. However, studies also concluded that this is not always the case with patients. Furthermore, studies have shown that protoporphyrin is normally eliminated in the feces and may be detected there. In addition to this, studies have also shown that urine is normally considered to be normal; however, there may be times when abnormalities are found in patients who have cholestasis or protoporphyrin hepatopathy. Some studies have also shown that it is possible to prove that there is an unusually high amount of coproporphyrin isomer I in the urine. Researchers have also found that FECH gene deficiency can be found in many organs at levels lower than 50% of normal, or between 10 and 30%. [17] There are several levels of FECH deficiency that may be found in different tissues.In more recent years, several studies have also shown that EPP can be passed down from one generation to the next through an X-linked dominant pattern.[18] Researchers have also found that people with this condition have normal FECH activities, but their erythrocyte total protoporphyrin levels are much higher than those of people with other types of EPP. Other than this, studies have also concluded that patients who have this condition also have a higher risk of acquiring problems connected to EPP. Studies have shown that approximately forty percent of the total quantity of protoporphyrin that may be found in their erythrocytes is comprised of zinc-protoporphyrin. This significant amount of zinc-protoporphyrin suggests that the accumulation of protoporphyrin occurs as a result of the supply of both of its metal substrates, Fe2+ and Zn2+, being rate-limiting. For the synthesis of protoporphyrin, both of these metals are necessary. One of the distinctive characteristics of this kind of EPP seems to be an increase in erythrocyte zinc-protoporphyrin in combination with a considerable increase in free protoporphyrin.[19,20]

The prevalence of microcytic anemia in patients ranges from twenty percent to sixty percent. Erythropoiesis was shown to be impaired in the vast majority of patients who had dominant EPP in the United Kingdom and France.[19,20] Although everyone had a decrease in their hemoglobin (Hb), the men were only slightly more anemic than the women. Iron storage, as assessed by serum ferritin (sFn), were decreased by two-thirds; yet, normal serum soluble transferrin receptor-1 and iron concentrations demonstrated that erythropoiesis was not constrained by iron supply. sFn is a serum protein that measures iron storage. A deficiency in FECH in EPP seems to lead to a stable condition in which there is decreased erythropoiesis, which is compensated by reduced iron absorption and supply. This state may be thought of as an equilibrium. This process may be partially mediated by protoporphyrin, which is an abbreviation for the compound protoporphyrin.[20]

DIFFRENTIAL DIAGNOSIS [21,22,23]

1. “Phototoxic Drug Reaction
2. Hydroa Vacciniforme
3. Solar Urticaria
4. Polymorphic Light Eruption
5. Discoid Lupus Erythematosus
6. Sunburn”

PROGNOSIS [24]

Studies have shown that unless hepatopathy happens because of the hepatotoxic effects of protoporphyrins, which damage the liver, the life expectancy for people with EPP is usually fine. Although the EPP gene rally has a significant impact on life quality, it does not reduce life expectancy. Because the pain that follows photosensitivity is severe and sudden, it is essential for the patient to make adjustments to their way of life and their occupation.[24]

COMPLICATION [25]

1. Fatal
2. Hepatopathy
3. Peripheral Neuropathy
4. Respiratory Failure
5. Thickenned skin of face , dorsum of hands (Knuckles)
6. Lichen reaction
7. Loss of lunuale of fingernails
8. Osteroporosis

MANGEMENT

1. Mangement of Photosensitivity

Studies have concluded that, in order for treatment of photosensitivity to be effective, management of the condition is necessary. Avoiding direct or indirect exposure to sunlight is the most effective method for minimizing red light reactions in EPP patients. This includes any exposure that takes place via windows, such as when a person is driving a car. In addition, it is strongly suggested that you protect yourself from the sun by using sunscreen and dressing appropriately (gloves, hats, and glasses). Because they protect against both visible light and long-wave radiation, physical sunscreens are more effective than chemical ones. One kind of UV radiation is known as long-wave radiation. Compresses made of wet (cold) water that are applied to the areas that are affected are one method that is used in the management of photosensitivity reactions. Although topical corticosteroids may be prescribed, they often have little effect. When required, non-steroidal anti-inflammatory drugs or red corticosteroids may be used in the treatment that is taken orally. Beta-carotene has seen a lot of use recently as a treatment option for EPP patients in order to increase their tolerance to light. Patients have said that they felt some improvement as a consequence of using this treatment method. Children should take 90–120 milligrams (mg) of beta-carotene per day, while adults should take 180–300 milligrams (mg) per day. On the other hand, recent studies have shown that there is an inverse link between carotenoids and lung cancer, and this relationship is predominantly seen in smokers.[26,27]

Studies have concluded that other treatment approaches include the oral delivery of vitamin C and vitamin E, as well as the oral administration of cysteine in dosages of 500 mg twice daily. Antihistamines, notwithstanding the possibility that they may have a phototoxic effect, provide an additional viable treatment option. With the exception of beta-carotene, the effectiveness of all of these treatment approaches has not been shown in a way that can be considered definitive.[28] The duration of therapies that are designed to improve photosensitivity is closely tied to the ratio of risk to benefit that may be obtained by certain patients. This ratio may be obtained by testing the patients' blood levels of certain proteins. UVB/NBUVB phototherapy, or PUVA, may be used in order to encourage tanning and improve sun tolerance. The duration of the treatment is limited by the criteria for phototherapy, and it is also dependent on the patient benefit obtained in terms of a decrease in photosensitivity.[29] An alpha-melanocyte-stimulating hormone analogue known as afamelanotide is responsible for the increased synthesis of melanin in the epidermis. It was only recently shown to have beneficial advantages in patients who have EPP, which is a very new discovery.[30]

2. Reduction of Protoporphyrin Levels

a. Reduction of Erythropoiesis

Studies have concluded that the "outcomes of the studies suggest that in order to achieve this goal, either exchange transfusion or hypertransfusion may be used. Haematin synthetic may alter the ALA synthase enzyme, which is the rate-limiting first enzyme in the haematin synthetic pathway, in order to temporarily suppress erythropoiesis. On the other hand, it is not fair to think of this technique as a treatment for the disease on a long-term basis".[31,32,33]

b. Cholestyramine

Studies have concluded that "it may be used to facilitate the increased elimination of excess protoporphyrin via the biliary system. It prevents protoporphyric hepatopathy by binding the excessive protoprophrin, which leads to an increase in the protoprophrin's elimination via feces, a decrease in the protoprophrin concentration in plasma and red blood cells, and so on. Between 4 and 16 grams of cholestyramine per day is the suggested daily dose. Chenodeoxycholic acid and ursodeoxycholic acid are two more drugs that, like this one, are thought to be similar to one another".[34,35,36]

3. Management of Microcytic Anemia

Studies have concluded that the declining trend in hematologic parameters was positively connected with the quantity of erythrocyte PPIX. The patients tested showed mild microcytic anemia and thrombocytopenia. It is important to point out that the serum iron levels of the patients were normal, as were their levels of soluble transferrin (Tf) receptor (sTfR). This demonstrates that the supply of iron does not seem to be a limiting element for the erythropoiesis process. It is not advised to supply patients with oral iron since trying to treat the mild anemia found in EPP patients is generally futile. On the other hand, intravenous iron supply or even blood red fusion could be examined in EPP patients who have a more marked red.[37]

4. Management of Liver Disease

Studies have concluded that the only treatment now available for liver disease that has progressed to its last stage is a transplant of healthy liver tissue. Studies have also concluded that it was supplied to a patient for the first time in 1980 who suffered from EPP.[38] Furthermore, studies have concluded that patients with EPP who are suffering worsening liver disease may benefit from undergoing liver transplantation as a treatment option. In addition to this, studies have also concluded that only by removing the affected liver can this condition, which ought to be regarded as a medical emergency, be cured. In conclusion, research has shown that liver transplantation has no effect on the clear consequences of having insufficient FECH and producing too much proporhyrin. Studies have also concluded that patients diagnosed with EPP will thus continue to present the typical symptoms, and they will be at risk for the same outcomes in the future. Several other studies have found that bone marrow transplantation should be considered. In fact, sequential liver and bone marrow transplantation should be thought of as the best treatment, as it has been done successfully in the past.[39,40] This treatment has already been carried out with success; therefore, it ought to be considered the best. In addition to this, bone marrow transplantation is something that must be taken into account.

CONCLUSION

We have come to the conclusion that EPP is a hereditary disorder caused by a mutation in ferrochelatase, the last enzyme in the heme biosynthesis cycle. While treating these patients, the dermatologist, psychiatrist, primary doctor, and gastroenterologist must work together as a team. Specialty-trained nurses may also assist by advising the patient on photoprotection, directing medical care, and monitoring for problems. Close communication between members of the interprofessional team is essential for improving results. The identification of new pharmacologic ligands capable of correcting or assisting UROS mutant folding by inhibiting their detection by the quality control system might be a viable therapeutic strategy for CEP. However, further progress in understanding the biochemical mechanism of UROS enzymatic insufficiency, as well as the molecular etiology, is necessary for new effective CEP therapeutic approaches.

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