



Case Report

An Extremely Rare Case of Congenital Erythropoietic Porphyria Diagnosed In Adulthood with Unusual Life Threatening Complications

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Abstract

Congenital erythropoietic porphyria (CEP) is an autosomal recessive inborn error of heme synthesis that results from the markedly deficient activity of uroporphyrinogen III synthase (UROS). We describe a 44-year-old male with history of passing red urine since infancy, progressive blistering and scarring of the skin and severe hemolytic anemia. After years of skin damage, his face is mutilated; hands are deformed, he has scleromalacia and prominent areas of hypertrichosis and skin darkening. Patient presented to us in shock with severe anaemia and derangement of haepatorenal and coagulation profile. Uroporphyrin 1 and coproporphyrin 1 levels were markedly raised in urine. Patient was stabilized with intravenous fluids, hematinics and blood transfusion. In spite of conservative treatment and photoprotective measures patient's lesions are progressing. Bone marrow transplantation and/or gene therapy are proposed as the next steps in his treatment.

Keywords: *Congenital erythropoietic porphyria, Porphyrins, Anaemia, Scleromalacia.*

INTRODUCTION

The inherited porphyrias are disorders of heme biosynthesis resulting from the deficient activity of a specific enzyme of the heme synthetic pathway. ^[1] Depending on the site of predominant porphyrin accumulation, the porphyrias are

grouped into the following two types: erythropoietic and hepatic. ^[2] The following three different erythropoietic porphyrias (EP) have been reported: erythropoietic protoporphyria (EPP, MIM 177000), congenital erythropoietic porphyria (CEP, MIM 263700), and

hepatoerythropoietic porphyria (MIM 176100). CEP or Günther's disease is an autosomal recessive disease resulting from deficient uroporphyrinogen III synthase (UROS) activity^[1] It is a severe deforming type of porphyria having multiple oculocutaneous and systemic manifestations. The reported complications include chronic hemolysis, severe anemia, hypersplenism, bone marrow dysplasia and disfiguring oculo-cutaneous stigmata.^[3]

CASE REPORT

A 44 year old man with scarred face and deformed hands presented with the episode of profuse bleeding from nostrils. Regarding morbid skin he revealed that it started with blistering over photoexposed sites since the age of two years (as noticed by mother). Progressive blistering, ulceration, and scarring of face and extremities resulted in disfigurement and altered pigmentation. In spite of extensive damage patient never took specialist consultation due to poverty and illiteracy. Recurrent episodes of profuse bleeding and fainting attacks made him bed ridden for the past three months. Patient was aware of passing red colored urine since childhood. There was no history of fever. At the time of examination he was in shock with PR 116/min, BP-74/50 along with marked generalized pallor. Striking features like mottled pigmentation, mutilated scars and hypertrichosis were observed on cutaneous inspection (Figure 1 and 2). He had mitten hands with resorption of distal phalanges and anonychia (Figure 3). Patient had diminished vision, scleromalacia and scleral ulceration on ocular examination (Figure 4). Rest systems were normal on clinical evaluation. Patient's urine was dark brown in colour (Figure 5) and orange red fluorescence was noticed on wood's lamp examination (Figure 6). With clinical possibility of CEP, porphyrin studies were performed which revealed markedly high levels of uroporphyrin I and isocoporphyrin I in urine. We couldn't perform genetic studies/detailed analysis of more

specific type of porphyrins in plasma, RBC and stool due to unavailability of these tests and poor affordability by patient. Based on the time of onset of classical symptoms, clinical signs, increased uroporphyrin 1 and coproporphyrin 1 in urine and absence of neurological symptoms our patient was diagnosed with CEP.^[5] Haematological and biochemical studies revealed picture of severe haemolytic anaemia, thrombocytopenia, with deranged coagulation and haepatorenal profile [Hb 4.6gm/dl, WBCs 14900, serum iron 13(n 65-175) and serum transferrin 6.10 (n=20-50). Platelet count was 76000/cumm and prothrombin time was prolonged. Renal profile showed urea 99mg /dl and creatinine 3.3mg/dl. His liver tests were deranged as SGOT-215 IU, SGPT-97 IU, alkaline phosphatas-999 IU. Although patient was alcoholic but viral screen for hepatitis and HIV was negative. X-rays of hands and feet reported erosive arthritis with acrolysis, osteopenic changes and shortening of distal phalanges. Ultrasonography showed bilaterally small kidneys and hepato-splenomegaly with minimal ascites. Cardiac evaluation detected concentric left ventricular hypertrophy and right ventricular diastolic dysfunction with minimal pericardial effusion. Conservative management was done and strict photoprotective measures were explained to the patient. Patient was attached to department of Dermatology and Internal Medicine for further follow up.



Figure 1: Hypertrichosis over face, chest alongwith scarring of hands and face.



Figure 2: Crusting, altered pigmentation and mutilating scarring.



Figure 3: Shortened and deformed fingers



Figure 4: Scleromalacia with ulceration.

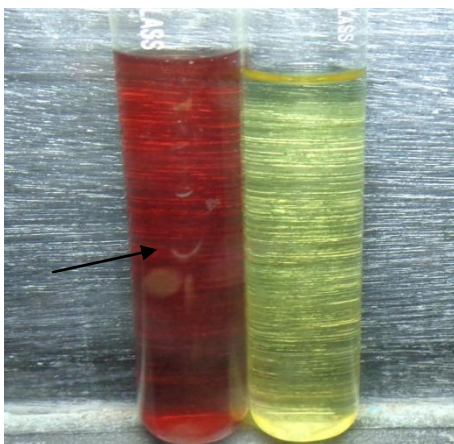


Figure 5: Brown red colored urine

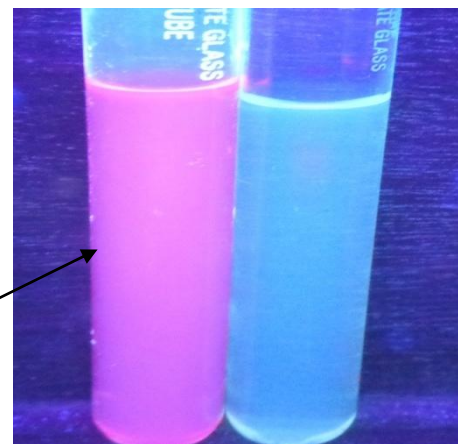


Figure 6: Pink/orange red fluorescence under woods lamp examination of urine.

DISCUSSION

CEP has an estimated frequency of 1 in every 2 to 3 million people. CEP is a very rare disease with only approximately 200 patients reported worldwide.^[3] CEP is a disorder of heme biosynthesis with complete inhibition UROS III activity which results in overproduction of isomer I porphyrins (uroporphyrin I and coproporphyrin I). The profound isomer III porphyrin deficiency leads to chronic anaemia even hydrops fetalis in utero. Further lifelong overproduction of isomer I porphyrins produce oculo-cutaneous and systemic manifestations. Blistering, fragility and scarring of exposed oculocutaneous sites lead to mutilating deformities.^[4] Chronic hemolytic anemia induces hypersplenism and bone marrow hyperplasia. Clinically patient can present with hepatosplenomegaly, osseous fragility (osteopenia and osteoporosis) and acral osteolysis.^[4] Long-term cutaneous sequelae include scarred mutilated face, mitten hands, hypertrichosis and non-melanoma skin cancers.^[3] Case reports describing such manifestations are there in literature. We couldn't find any case with life threatening consequences of CEP like deranged coagulation profile, cardiac involvement along with involvement of hemodynamic and hepatorenal systems. In addition to progressive disease (CEP), patient was chronic alcoholic which made his illness more critical by deranging his coagulation profile secondary to liver involvement. Frequent episodes of profuse blood loss not only increased severity of anaemia but also compromised hemodynamic status which resulted in pre-renal failure along with high output cardiac failure.

Cicatricial ectropion, corneoscleral scarring and lagophthalmos are frequent ocular manifestations of CEP. Our case had profound bilateral scleromalacia which is a rarely reported complication.^[5] The clinical diagnosis of CEP is confirmed biochemically by elevation of uroporphyrin I and coproporphyrin I levels in urine and plasma samples. Fecal and erythrocyte samples contain high uroporphyrin, coproporphyrin, and protoporphyrin levels.

Further genetic studies reveals mutations in UROIII gene located on chromosome 10q25.2-q26.3.^[4] More than 49 mutations has described and the most common mutation is substitution of amino acid C73R that is associated with severe phenotype.^[6] We couldn't perform genetic studies and more detailed biochemical evaluation due to unavailability of these expensive investigations at our setup. The two main differential diagnoses are hepatic erythropoietic porphyria and erythropoietic protoporphyria. Hepatoerythropoietic porphyria (HEP) presents with similar symptoms in neonatal period but can be differentiated by absence of isocoporphyrin in urine or feces.^[7] In EPP acute skin symptoms (burning sensations, oedema, blisters, erythema and purpura) appear within minutes to hours. Further EPP has autosomal dominant inheritance (95% of cases) and there is marked elevation of protoporphyrins in erythrocytes.^[4]

Splenectomy, hypertransfusion, and orally administered drugs such as charcoal and cholestyramine, which binds porphyrins have also been used to treat CEP. Blood transfusion reduces endogenous porphyrin synthesis by negative feedback and also raises hemocrit levels thus play a dual role. Hydroxyurea is a chemotherapeutic agent used in severe cases to decrease production of endogenous porphyrins. Splenectomy is indicated for patients with splenomegaly with blood dyscrasias. Unfortunately, these classical treatments are unsatisfactory and do not effectively control the disease. Allogeneic bone marrow transplantation (BMT)/ gene therapy with hematopoietic stem cells (HSCs) are potential upcoming measures for severely affected patients.^[8]

CONCLUSION

CEP is a very rare metabolic disorder which is usually diagnosed in early childhood (Early onset type). Our case was early onset type but diagnosed in fourth decade of life with atypical presentation. A high clinical suspicion and active investigative workup is required to diagnose such cases. Further

bone marrow transplantation and gene therapy are proposed modalities of treatment.

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