Case report:

Congenital Erythropoietic Porphyria (CEP): A rare disease

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Abstract

Congenital Erythropoietic porphyria (CEP or Gunther disease) is a rare autosomal recessive inborn error of heme biosynthesis with a mutation in the gene that codes for uroporphyrinogen III synthase (UROS), resulting in severe loss of activity of UROS and elevations of uroporphyrin I and coproporphyrin I. This deficiency is associated with the accumulation of porphyrins and porphyrin precursors in the erythrocytes, plasma, and, urine which, in turn, causes blistering over sun-exposed areas and chronic severe photosensitivity. Here, we reported a 10-year-old boy, born of parents of consanguinous marriage presented with recurrent blistering over sun-exposed skin from the age of 2 and reddish urine from birth. There was erythrodontia, hyperpigmentation, atrophic scarring, hypertrichosis predominantly in the face and extremities, and deformities of fingers. Bright red fluorescence was noted in the urine and teeth under the wood's lamp. Histopathology revealed subepidermal bulla. Based on history, clinical examinations, wood lamp examination, and histopathology we diagnosed the case as congenital erythropoietic porphyria. We recommended absolute photoprotection, using high sun protection factor sunscreens, vitamin D supplementation to compensate for the lack of sun exposure, and psychotherapy to minimize the psychosocial impact.

Keywords: Congenital Erythropoietic Porphyria, Uroporphyrinogen III synthase (UROS), Cutaneous blistering, Subepidermal bulla

Introduction

The first documented human porphyria is congenital erythropoietic porphyria (CEP). It is related to the disturbance of the porphyrin metabolism.[1] Gunther defined the disease as 'haematoporphyria congenital' in 1911–12.[2] Congenital erythropoietic porphyria (CEP) is a rare genetic disease inherited as an autosomal recessive trait.[1-2] The main pathology is the remarkable deficiency of the fourth enzyme of the haem biosynthetic pathway, uroporphyrinogen III synthase.[3] This enzyme defect results in the accumulation of pathogenic porphyrin precursors, uroporphyrin I and coproporphyrin I.[1-3] The accumulation of porphyrins results in unique cutaneous manifestations, such as bullae and vesicles on sun-exposed regions of skin, scarring, erythrodontia, hypo or hyperpigmentation and hypertrichosis.[4] Visceral complication, hemolysis, and growth retardation are also reported to complicate the disease.[3-4] Congenital erythropoietic porphyria is an extremely rare disease; estimated prevalence is around 1 or less in 10,000,00 population.[5] To our knowledge, only one case was documented in Bangladesh before. However, another case of this rare porphyria was reported in Bangabandhu Sheikh Mujib Medical University Hospital (BSMMU), Dhaka, Bangladesh at the

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Cite this Article:
Chowdhury MAH, Malabeka S, Tahnin NAT, Uddin MJ, Islam MA. Congenital Erythropoietic Porphyria (CEP): A rare disease. Ban Acad Dermatol. 2023; 03 (02): 73-77

Available at: www.jbadbd.com
An official publication of Bangladesh Academy of Dermatology (B.A.D.)

outpatient department of Dermatology & Venereology in 2023.

Case report

Our patient is a 10-year-old boy who presented to the outpatient department of the hospital with complaints of reddish urine from birth and recurrent blisters over sun-exposed skin from the age of two. Blisters were tense and non-itchy, prominent over the dorsum of hands, feet, and face which were exacerbated by exposure to sunlight. Some blisters ruptured to form erosion, and some became ulcerated, leaving atrophic scar and hypopigmentation on healing. Since birth, his parents noticed red urine staining the diaper without any noticeable discomfort during micturition. Parents also noticed eruption of red teeth at the age of 1 year of their child. The patient was born into a consanguineous marriage. He had one younger brother who was healthy. Both his parents were phenotypically normal. His gestational period and delivery remained uneventful. He was reported to be healthy at birth, made normal progress, and achieved age-appropriate developmental milestones. The boy was vaccinated as per the national EPI schedule. A detailed history revealed that the child had multiple visits to the local doctor for his complaints and was given multiple antibiotics without any significant improvement. He lives with his family and comes from a low socio-economic status.

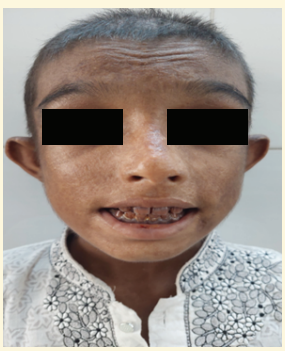

Fig. 1: Erythrodontia

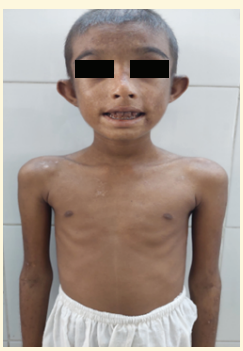

Fig. 2: Scarring, hypopigmentation, and hypertrichosis

The complete general examination showed that the patient was well-oriented with normal vital parameters. The patient was anemic and had reddish teeth, and facial scars with thin, sparse hair. There were multiple atrophic scars, hypo, and hyperpigmented macules over the face, dorsum of hands, feet, and V area of the chest and back with facial hypertrichosis. No intact blisters were found, but there were some erosions and crusting more marked over the dorsal hands and elbow. There was flexion deformity of the distal interphalangeal joints of both hands. There was discoloration of toenails with increased nail fragility and subungual hyperkeratosis of great toenails. However, the fingernails were normal. He had a soft, non-tender abdomen with a just palpable spleen. All other systems revealed no abnormality. Based on the history and clinical examination, our primary diagnosis was congenital erythropoietic porphyria.

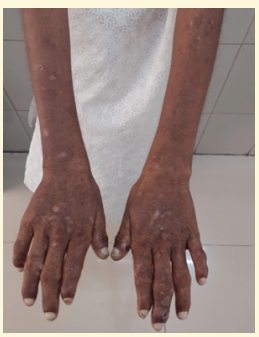

Fig. 3: Atrophic scarring, hypopigmentation, crusting and deformity of hands

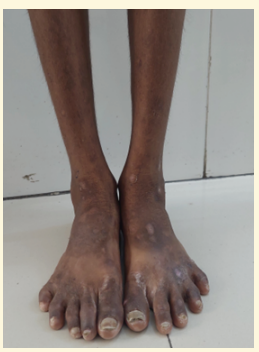

Fig. 4: Atrophic scarring and nail changes of both feet

To assist with the clinical diagnosis, further laboratory investigations were performed to confirm the diagnosis. Wood's lamp examination revealed coral red fluorescence of teeth and urine. Lab investigation revealed moderate microcytic hypochromic anemia, Moreover, a higher red cell distribution width (RDW), and a normal white blood

cell and platelet count. The peripheral blood film revealed microcytic hypochromic red blood cells (RBCs) with anisopoikilocytosis, few target cells, and marked rouleaux formation. Ultrasonography revealed splenomegaly without hepatomegaly. Histopathology revealed subepidermal bulla, dermal edema, extravasated RBC, thickened and hyalinized dermal blood vessels which were suggestive of erythropoietic porphyria. Porphyrin levels were not measured and genetic testing was not performed due to unavailability.

Fig. 5: Red urine

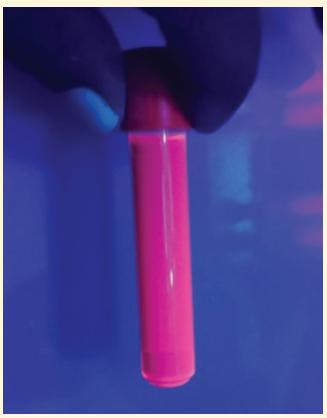

Fig. 6: Coral red fluorescence of urine

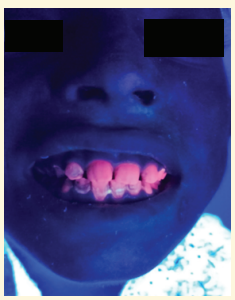

Fig. 7: Coral red fluorescence of teeth

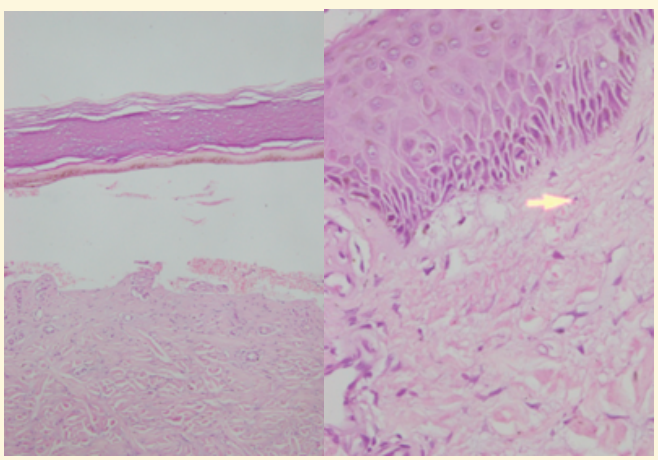

Fig.8: Sub-epidermal bulla, dermal edema, extravasated RBC, thickened and hyalinized dermal blood vessels with few chronic inflammatory cell infiltrates in the dermis.

Discussion

CEP is a very rare form of porphyria inherited by an autosomal recessive trait that causes the skin to be highly sensitive to sunlight.[5] The underlying defect is mutations of two allelic genes encoding the enzyme uroporphyrinogen III synthase that leads to the accumulation of the porphyrin precursors, coproporphyrin I and uroporphyrin I.[6] The C73R mutation is the most frequently mutated genes. The co-inheritance of gain of function mutation in ALAS2 can lead to a more severe phenotype.[7] The accumulated precursor porphyrinogens are spontaneously oxidized to their corresponding porphyrins. These porphyrins are biologically inert but cause cutaneous features especially photosensitivity which leads to the formation of blisters, erosions, scarring, and mutilating deformity of photo exposed skin.[6-7] These porphyrins are released from the maturing erythrocytes into the plasma and are excreted in urine, thereby producing a reddish color urine.[7] The primary dentition of patients with CEP shows a deep red-brown discoloration due to porphyrin accumulation.[7-8] Porphyrin concentration is much higher in the dentin than in the enamel due to the affinity of porphyrins to calcium phosphate.[8] The reddish-brown color of urine together with red teeth is the characteristic feature for early diagnosis of CEP.[8] CEP presents soon after birth, but uncommonly may present in adulthood. Symptoms that appear in adulthood tend to be milder than symptoms that begin early in life.[7-8] In our context, the 10-year-old boy manifested the symptoms since birth with red urine. Characteristic erythrodontia was present of both permanent and deciduous teeth since its eruption. Photosensitivity started from the age two which also suggested the early childhood manifestations of the disease. However, photo- sensitivity was not severe enough to cause immediate pain and burning leading to screaming when exposed to sun. Blistering and scarring were more marked on the photo exposed area with limited involvement of scalp. In severe cases, ectropion with corneal damage and loss of vision may result.[9] But in our case the child did not complain any eye symptoms, probably due to less severity of the disease. Hypertrichosis of the cheeks and long eyelashes were evident. Atrophic scarring was present on dorsal hands and face with flexion deformity of fingers without any mutilating scar. Onset at birth, absence of GIT and neurological symptoms (seizure,

psychosis) aided us to exclude other variants of porphyria (porphyria cutanea tarda, variegate porphyria, erythropoietic porphyria).

Systemic features of CEP include growth retardation, hemolytic anemia, thrombocytopenia, porphyrin gallstones, organomegaly, osteopenia, and increased rate of fracture.[10] However, in our case patient did not have any growth retardation and achieved developmental milestones in time. He had microcytic hypochromic anemia, probably due to iron deficiency which could be a cause of nutritional deficiency, as nutritional anemia is more prevalent in developing countries among those with low socio-economic status.[10] The Patient had splenomegaly without hepatomegaly. Apart from anemia and splenomegaly, he didn't have any other systemic features. Wood's lamp examination of both urine and teeth showed coral red fluorescence, which is a unique and characteristic feature of CEP. This unique finding led us to diagnose the disease in the very first place. Skin biopsy showed subepidermal bulla and extravasation of RBC which was consistent with the biopsy findings of CEP. However, the porphyrin assay, which is an important diagnostic marker for CEP, could not be performed due to unavailability. Moreover, the severity of the disease is directly related to the plasma porphyrin level and the residual activity of UROS. Abnormal and high levels of uroporphyrin I and coproporphyrin I are found in urine, stool, and RBC.[8-10] Therefore, in our patient severity of the disease could not be determined. But clinically it seemed to be a case with mild to moderate severity. Therefore, based on the characteristic's clinical findings, laboratory investigations, wood's lamp, and biopsy findings we have labeled the case as CEP.

Treatment of CEP is challenging and there is no standard therapy exists. Treatment is based mainly on the clinical manifestation. Currently, the only curative treatment option is allogeneic bone marrow transplantation.[9-11] In patients who do not undergo this procedure, strict avoidance of sunlight use of sunscreens containing zinc oxide or titanium oxide, vitamin D supplementation, and use of sunglasses to avoid ocular complications is the mainstay of therapy. Other options include activated charcoal, presumably impairing the absorption of endogenous porphyrins, phlebotomy, and repeated transfusion of packed RBC to maintain the hematocrit level.[10-12] In some patients with hypersplenism and excessive circulating RBC trapping and destruction, splenectomy may reduce the need for transfusions.[11-12] In our case, since the patient had mild to moderate symptoms, we opted for general management options which include, sun avoidance, the use of sunscreen, vitamin D and Zinc supplementation. The patient was advised for regular follow-up to observe the course of the disease and assess the prognosis.

We understand that early detection of CEP symptoms is crucial for accurate diagnosis and treatment. Careful observation and diagnostic approach can help us to differentiate it from other overlapping porphyrias at an early stage. It is also important to note that CEP is a lifelong condition, and patients will require lifelong monitoring. Recognizing the disease at its earliest stages is important to assist clinicians in providing appropriate patient-centered treatment and to address the quality of life by educating and counseling on preventive measures and providing psycho-social support.

Conclusion

CEP is a very rare form of porphyria. Therefore, we reported this case to highlight the varied clinical presentation and useful diagnostic approach despite having limitations in performing porphyrin assay and genetic testing. We understand this can aid in raising awareness among fellow clinicians. We hope our findings can further advance the understanding of this rare disease and treatment options. The rarity of the disease and the chance of under-reporting prompted us to present this case report.

Conflict of Interest

None

Funding source

None

Patient Consent

Taken

IRB approval status

Not applicable

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