

Congenital erythropoietic porphyria: A case series of a rare uroporphyrinogen III synthase gene mutation in Nepalese patients



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Key words: congenital erythropoietic porphyria; L139R mutation; Nepal; uroporphyrinogen III synthase.

INTRODUCTION

Congenital erythropoietic porphyria (CEP) is an autosomal recessive cutaneous porphyria caused by mutations in the gene coding for uroporphyrinogen III synthase (UROS).^{1,2} Phototoxic reactions result from the accumulation of biologically inert type I porphyrins, predominantly in the skin, red blood cells, bones, and teeth.

CEP is a rare genetic disease, affecting less than 1 in 1,000,000 children, with only approximately 280 cases reported in the literature, primarily in Western countries.^{3,4} We report 3 cases of Nepalese female patients with characteristic clinical features, supportive laboratory panels, and a rare genetic study finding. To our knowledge, these findings have been rarely reported in the literature, and this is the first case report or series of CEP reported in Nepal.

CASE SERIES

Case 1

A 17-year-old female (now 37 years old), born from a nonconsanguineous marriage, presented with a history of spontaneous blistering over photoexposed areas, starting in the first few days of her life. The lesions healed with scarring that led to progressive deformities of her hands, ears, and nose by 18 years of age. Her mother reported a red discharge in her diaper and redness and matting of both eyes since early childhood. She gradually developed deformities of her eyelids, making it difficult to close them fully. Three of her 7 siblings were similarly affected. Two of the affected siblings died shortly

Abbreviations used:

CEP: congenital erythropoietic porphyria
UROS: uroporphyrinogen III synthase

after birth, and a third, her older sister (case 2), died at the age of 24. Both parents were phenotypically normal.

Examination revealed thickened skin, hypopigmentation and hyperpigmentation, and scarring at photoexposed sites (Fig 1, A); facial hypertrichosis; and reddish-brown tooth discoloration and disfiguration of the nose, ears, and fingertips bilaterally to the proximal interphalangeal joints. Eye examination revealed severe ectropion, trichiasis, and scleral melting (Fig 1, B). Abdominal examination revealed an enlarged spleen 4 cm below the left costal margin. Blood investigation showed pancytopenia, elevated erythrocyte sedimentation rate, positive creatinine-reactive protein, a normal serum iron profile, and an abnormal porphyrin profile (Table I).

Case 2

The older sister of case patient 1 presented at the age of 18 years with photoinduced skin blistering of the face and extremities since her sixth day of life. She had associated progressive deformities of her bilateral hands and feet, bilateral ears, and nose. She reported having had photophobia and diminished vision in the right eye since early childhood. Examination revealed sclerodermatous changes and hypopigmented and hyperpigmented scars over

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Funding sources: None.

IRB approval status: Not applicable.

Reprints not available from the authors.

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JAAD Case Reports 2021;10:102-6.

2352-5126

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<https://doi.org/10.1016/j.jidcr.2021.02.017>



Fig 1. A, Thickened skin with hypopigmentation and hyperpigmentation and scarring over photoexposed sites, facial hypertrichosis, and reddish-brownish discoloration of the teeth. **B,** Severe ectropion, trichiasis, and scleral melting.

Table I. Results of laboratory investigations

Parameter (normal range)	Case 1	Case 2	Case 3
Urine total porphyrin (25-144 nmol/L)	11,986 nmol/L	NA	13,269 nmol/L
Fecal porphyrin (10-200 nmol/g)	5569 nmol/g	NA	1797 nmol/g
Plasma porphyrin (<11.2 nmol/L)	NA	NA	1120.5 nmol/L
Plasma porphyrin peak	618 nm	NA	618 nm
Erythrocyte porphyrin (0.4-1.7 μ mol/L)	35.8 μ mol/L	NA	26.2 μ mol/L
Total white blood cell count (4000-11,000/mm ³)	1700/mm ³	3600/mm ³	4500/mm ³
Platelets (150,000-450,000/mm ³)	107,000/mm ³	150,000/mm ³	175,000/mm ³
Hemoglobin (female: 12.0-15.5 g/dL)	9.4 g/dL	8.7 g/dL	12 g/dL

the face and extremities (Fig 2, A); partial absorption of both ears; and brownish-pink-colored teeth. Hypertrichosis over the face and arms was present, and the bilateral extremities showed sclerodermatous contracture and acro-osteolysis (Fig 2, B). Ectropion and bilateral keratoconjunctivitis were apparent. She had mild anemia and splenomegaly. Porphyrin profiling and genetic analysis were not performed because of the unavailability of laboratory facilities at that time. She died at the age of 24 from a secondary infection.

Case 3

A 35-year-old woman, born to phenotypically normal parents, presented with progressive bilateral deformities of the hands and photoblistering since birth, with resulting dyspigmentation, scarring, and sclerodermatous changes of the face and distal extremities (Fig 3) and progressive deformities of both hands. She had a history of recurrent keratoconjunctivitis and complications requiring enucleation of her left eye (Fig 3). Facial hypertrichosis, microstomia (Fig 3), erythrodontia, and mutilations of both hands were evident on examination.

Laboratory reports revealed a normal complete blood count but an abnormal porphyrin profile (Table I).

Wood's lamp examination revealed pink-red fluorescence of the urine and teeth in all 3 patients. In case patients 1 and 3, sequencing of the UROS gene, exons 1 to 10 including flanking intronic regions, showed a homozygous transversion of T to G at nucleotide 416 in exon 7 (c.416T>G) leading to an L139R protein substitution at the terminal of the β 6 protein chain.

The patients were advised to use strict photoprotection, emollients, and vitamin D supplementation. They were also counseled about the disease, the need for long-term follow-up, wound care, and lifestyle modifications.

DISCUSSION

CEP is a multisystem disorder resulting from the accumulation of phototoxic water-soluble porphyrin intermediates (coproporphyrinogen I and uroporphyrinogen I). The inherited defect in the heme biosynthesis pathway is characterized by decrease in UROS activity (from <1% to approximately 10% of

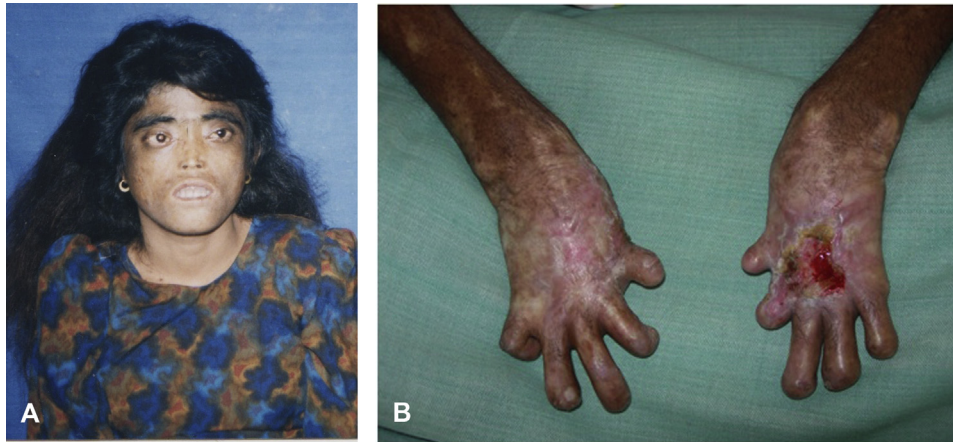


Fig 2. **A,** Sclerodermatous changes and hypopigmented and hyperpigmented scars over the face. **B,** Acro-osteolysis and contracture of the bilateral hands.



Fig 3. Dyspigmentation, scarring, and sclerodermatous changes over the face with enucleation of the left eye.

normal).⁴ The decrease occurs as a result of either biallelic UROS gene pathogenic mutation with autosomal recessive inheritance or, less commonly, via homozygous GATA1 pathogenic mutation with X-linked inheritance.⁴ Although we did not perform parental genotyping, it is likely that our 3 subjects had an autosomal recessive inheritance of their disease, given the absence of clinical manifestations in the older generations and the mutation identified in the UROS gene. According to the Human Gene Mutation Database (HGMD, <http://www.hgmd.org>), to date only 51 different mutations in the UROS gene causative of CEP have been reported. The majority of these mutations are missense mutations and are

mostly reported in the Caucasian population.⁵ c.217T>C is the most frequently reported mutation in Caucasians, followed by c.10C>T and c.683C>T.⁴ These 3 mutations together constitute around 46% of all mutations identified. However, these mutations are not very common in Asian populations. There is a paucity of data on UROS gene mutations in Asian countries, especially South Asia, and they seem to be different from those in Western populations.⁶ Two novel mutations, c.386C>T and c.184A>G, were identified in the Japanese population. Other mutations include a c.7G>T mutation seen in a Japanese family and a c.11,776 G>T mutation in a Vietnamese patient. Both of these mutations led to valine to phenylalanine substitution at codon 3 (V3F).⁷⁻⁹ Pandey et al¹⁰ reported c.569C>T and 710T>C mutations in Indian patients. Moghbeli et al¹¹ reported c.139T>C and c.710T>C mutations in Iranian patients. Gao et al¹² reported a unique c.416T>G mutation in a Chinese patient similar to ours.

Some genotype–phenotype correlations are well established in CEP. For example, the c.217T>C mutation is associated with more severe disease and poor prognosis. The GATA1 gene mutation is associated with a sex-linked pattern of inheritance, the hematologic phenotype of beta thalassemia intermedia, and marked thrombocytopenia.¹³ Mild hematologic manifestations seen in all of our patients, similar to those in the Chinese patient with c.416T>G mutation,¹² may signify a probable correlation. However, given the lack of overall consistency in genotype–phenotype correlations, other factors, including environment, photoprotective behavior, and unknown genetic components, have been considered as contributors.^{1,5}

The clinical presentation of CEP is phenotypically heterogeneous and of varying severity. Severe

cutaneous photosensitivity usually begins shortly after birth or in early infancy. However, current literature suggests that the age of onset ranges from 30 weeks of gestation to 60 years of age.^{1,14} Increased friability and blistering of the epidermis over light-exposed areas are characteristic findings. Photoexposure may be associated with burning, itching, tingling, or pinprick sensations and development of signs such as erythema, blisters, and mild swelling of the lips and skin.¹

Recurrent blistering and secondary infections eventually lead to cutaneous scarring and sclerodermatous changes with areas of hypopigmentation and hyperpigmentation.⁵ As evident in our cases, hypertrichosis of the face and extremities, along with progressive deformities of the eyelids, nose, and ears and mutilation of digits, is characteristic.^{4,5} Ocular manifestations may include scleral necrosis, necrotizing scleritis, seborrheic blepharitis, keratoconjunctivitis, and sclerokeratitis.⁵ Noncutaneous symptoms associated with exposure to direct sunlight can last for up to 24 hours and may include excess tears, photophobia, rhinorrhea, headache, vasovagal symptoms, diarrhea, and vomiting.¹ Milder symptoms of photophobia and headache were reported by our patients; however, other noncutaneous manifestations were not evident. Other distinctive manifestations include erythrodontia along with microstomia, gum recession, dental caries, hepatosplenomegaly, and hemolytic anemia. Mild asymptomatic anemia to severe transfusion-dependent pancytopenia may be present. Bone loss due to demineralization and expansion of the hyperplastic bone marrow may be evident.¹⁴

Examination of teeth and urine samples shows a characteristic reddish-pink fluorescence under Wood's light.¹⁰ The diagnosis is supported by the porphyrin concentration profile in erythrocytes, urine, and stool, differentiating between isomers I and III for both uroporphyrin and coproporphyrin. The diagnosis is confirmed most commonly by identification of biallelic UROS pathogenic variants or rarely by the identification of a hemizygous pathogenic variant in the X-linked gene GATA1. However, with additional case reports, newer causative mutations are being identified.^{2,4}

The management of CEP is challenging. Prevention of primary manifestations with strict photoprotection along with vitamin D supplementation and frequent monitoring of hematologic indices remains the only applicable management strategy in the context of third world countries like Nepal, where gene therapy and newer drugs are not available. Bone marrow or hematopoietic stem cell transplantation can provide definitive

treatment; however, these are associated with significant morbidity and mortality.^{4,5} Patient-based managements such as frequent or chronic blood transfusions for significant hemolysis, splenectomy, and treatment with hydroxyurea to reduce bone marrow porphyrin synthesis have been tried. Gene therapy, proteasome inhibition, melanocortin-stimulating hormone analog (afamelanotide), and pharmacologic chaperone-based enzyme stabilization may be viable future therapeutic options.^{4,5}

The mean life expectancy of patients with CEP is 40 to 60 years.¹⁴ The quality of life for these patients can be quite poor, given the debilitating clinical features of the disease. The most common causes of death are secondary bacterial infection and severe hemolytic anemia. Early diagnosis and management by a multidisciplinary team of physicians, hematologists, dermatologists, and wound care specialists is recommended. Genetic counseling and prenatal diagnosis are valuable for risk reduction.

We thank Dr. Sharon Whatley, Porphyria Service, UK, for genetic analysis and Dr. Stephen Walker, London School of Hygiene and Tropical Medicine, UK, for advice and arranging for sample transfer.

Conflicts of interest

None disclosed.

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