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Case Report

Congenital erythropoietic porphyria five years observation with standard treatment: a case report

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Abstract

Porphyrias are a group of diseases characterized by a deficiency of enzymes in the haem biosynthetic pathway. Congenital Erythropoietic porphyria is a rare autosomal-recessive disorder lacking uroporphyrinogen III synthase. This inherited deficiency results in accumulating uroporphyrinogen I and coproporphyrinogen I in the bone marrow, skin, bones, and other tissues, ultimately excreted via urine and faeces. Clinical manifestations include severe photosensitivity on open body parts with blisters, scarring, hypertrichosis, and mutilations. We describe the first case of CEP in Armenia, with a diagnosis performed in Centre Francais Des (LBMR) Porphyries (France, Paris). It concerns a 22-year-old Armenian man suffering from photosensitivity, excessive hair growth, mutilation, and pink urine discolouration. The five years of follow-up have revealed worsening symptomatology despite preventative measures and demonstrate that standard recommendations did not alleviate the patient's deteriorating conditions. A cure with an allogeneic haematopoietic stem cell transplant is under strong consideration.

INTRODUCTION

Congenital Erythropoietic Porphyria, or Günther's disease, is a rare disorder characterized by severe photosensitivity and often with chronic hemolysis due to a defect of the fourth enzyme of the haem biosynthetic pathway, uroporphyrinogen III synthase (UROS). Inheritance is autosomal recessive due to biallelic *UROS* pathogenic variants, or more rarely, X-linked secondary to a hemizygous pathogenic variant of the *GATA1 gene* [1, 2]. An estimated prevalence of 1/1 000 000 in the general population and around 250 cases have been described worldwide. CEP affects males and females equally with no evident ethnic predisposition and has been described in various national groups. The primary supportive treatment measures include avoidance of sun exposure, vitamin D supplementation, and phlebotomy for mild cases, as iron deficiency may slow the biosynthetic haem pathway. In cases of severe intravascular hemolysis and pathophysiological sequelae of CEP, supportive red blood cell transfusion can be beneficial. In addition, the definitive cure with haematopoietic stem cell transplantation has been reported in the literature. We introduce the first Congenital Erythropoietic Porphyria in Armenia, with a biological diagnosis performed in LBMR Porphyries (Paris, France) and five years of observation.

CASE REPORT

This case report presents an interesting case of a 22-year-old man (currently 27) with CEP, born from a non-consanguineous marriage with sequelae including excessive hair growth, disfiguration of the fingers and ears, and pinkish-discoloured urine. Disease onset was at seven years of age following a vesicular rash of the face and upper extremities during outdoor play with sun exposure. He was admitted to a regional hospital and transfused red blood cells. He was followed by various dermatology clinics for ongoing investigation of his rash through childhood and adolescence until finally requiring suspension from the military service due to suspicion of cutaneous porphyria and its sequelae. In November 2017, the patient was consulted at the Haematology Centre. On examination, he had infected bullae on the face and hands with mutilated index fingers (Fig. 1), nose bridge (Fig. 2), violaceous gums (Fig. 3), hypertrichosis, and splenomegaly 3 cm below the costal margin. Additional history revealed that the patient had red urine (Fig. 4) and faeces. Therefore, metabolic Porphyrias, such as Congenital Erythropoietic Porphyria (CEP) or Hepatoerythropoietic Porphyria (HEP), were suspected. Laboratory investigation showed anaemia HGB-11.7 g/dl (N 13,0–18,0 g/dl), reticulocyte count 2,5% (N 0,2%–2,0%). Investigation for hemolysis and renal function via total bilirubin, haptoglobin, LDH, and creatinine were within normal range. Ultrasound of the abdomen revealed splenomegaly 19 cm in diameter. Diagnosis of CEP was confirmed via screening of porphyrins in erythrocytes, urine, plasma, and faeces, along with the low enzymatic activity of UROS in LBMR Porphyries (France, Paris). Total porphyrins in urine were significantly elevated with the prevalence of uroporphyrin I and coproporphyrin I. Porphyrins in faeces, plasma, and erythrocytes were also elevated, and the erythrocyte UROS enzyme activity

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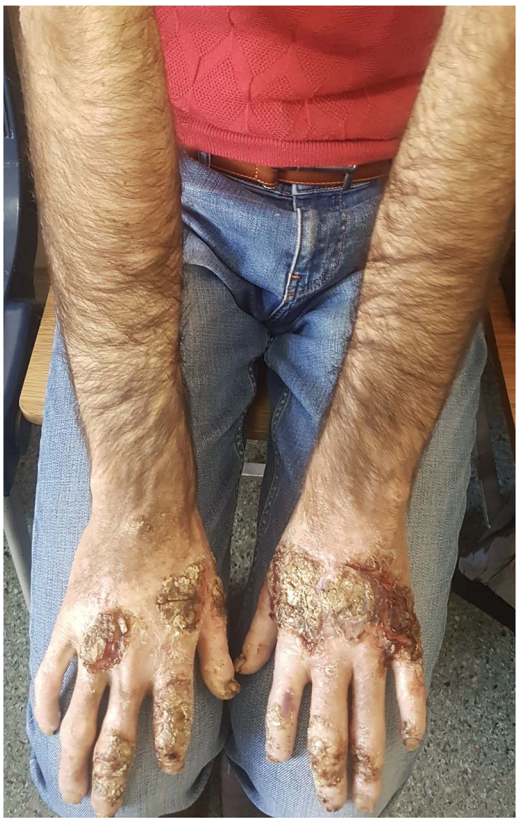

Figure 1. Hands with infected bullae and mutilated index fingers (2017).

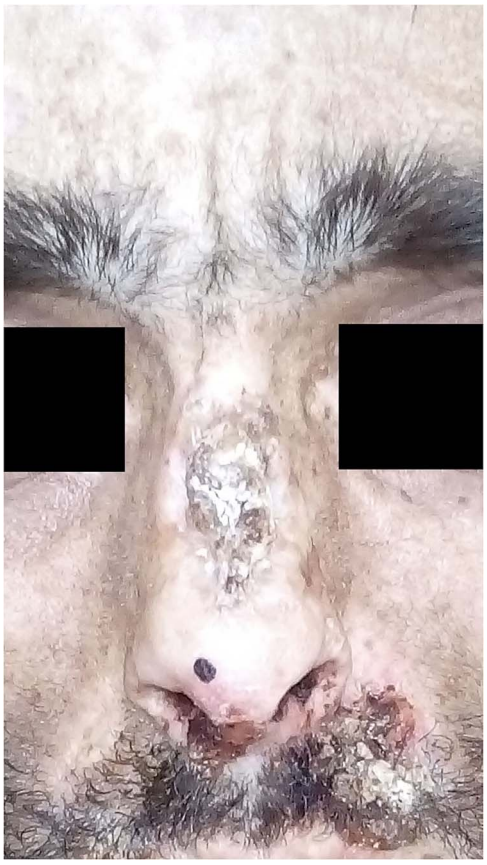

Figure 2. The mutilated nose bridge (2017).

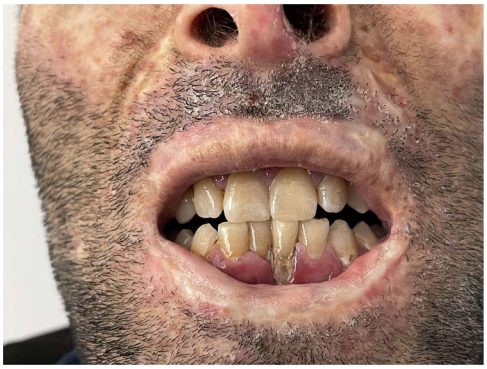

Figure 3. Porphyrins accumulation on the gums: erythrodontia (2023).

was decreased (2,0 U/mg Hb/h; N > 6,0). The abnormalities on the porphyrin profile (Table 1) and inadequate enzyme activity described supported a diagnosis of CEP. Management consisted of a multi-faceted supportive approach, including sunscreens SPF 50+, antibiotics, vitamin D supplementation, and phlebotomy. After ten days of antibiotics, the blisters had healed with scarring formation. Two phlebotomy procedures were performed, withdrawing 200 ml of blood with each twice monthly. Due to intolerance to repeated phlebotomy, our patient refused to move forward with further treatment. HSCT was suggested as a curative option, considering the patient had five siblings without clinical signs or symptoms of CEP. But the patient, with his family, refused the suggestion. Five years of follow-up with the described supportive care were accompanied by an ongoing significant deterioration of the patient's condition, such as amputation of the distal index and middle finger phalanges (Fig. 5). The destruction and deformation of the nose bridge nostrils (Fig. 6) and auricles (Fig. 7) continued to worsen. Our patient did not fare well during observation with initial supportive care. With the risk of further deterioration of his condition, intervention with HSCT remains a feasible and curative treatment option.

DISCUSSION

CEP is a rare erythropoietic porphyria, the aetiology of which is due to an inadequate UROS enzymatic activity in the erythroid precursors. The consequence is an accumulation of metabolically inactive uroporphyrinogen I and coproporphyrinogen I in the bone marrow, skin, spleen, bone, and other tissues excreted from urine and faeces. Porphyrin deposition in the skin dramatically worsens photosensitivity, resulting in characteristic dermatologic manifestations of this disease, including vesicular rashes, resultant scarring, skin thickening, focal hypo-/hyper-pigmentation and mutilations [2]. Recent findings demonstrate the unique role of fluorescent porphyrins in causing subcellular compartment-selective protein aggregation—porphyrin-mediated protein aggregation associated with nuclear deformation, cytoplasmic vacuole formation and endoplasmic reticulum dilation [3]. The onset of the disease is commonly from infancy to early childhood. Uncommon presentations consist of a mild illness that might be misdiagnosed with Porphyria Cutanea Tarda (PCT) and first appearance in adults often associated with myeloproliferative disorders [4]. The differential diagnosis of CEP includes porphyrias that present with photosensitivity. Of these differentials, HEP and CEP can be difficult to distinguish, given their similarities. However, HEP is a homozygous (or compound heterozygous) form of a familial (type 2) PCT due

Table 1. Porphyrin profiles in urine, faeces, erythrocytes, plasma

Specimen	level	Normal range	Unit
Urine porphyrins			
Total porphyrins	***8421**	<30	*nmol/mmol creat*
Total coproporphyrin	***1653**	<20	*nmol/mmol creat*
Coproporphyrin I	***98**	20-30	*%*
Total Uroporphyrin	***6217**	<10	*nmol/mmol creat*
Uroporphyrin I	***97**	70-80	*%*
Hexacarboxylporphyrin	0.7	<2.0	*%*
Heptacarboxylporphyrine	2.2	<3.0	*%*
Faeces porphyrins			
Total porphyrins	***6307**	<200	*nmol/g dry weight*
Protoporphyrin	***1.0**	70-75	*%*
Coproporphyrin	***96.2**	25-30	*%*
Isocoproporphyrin	0.1	<1.0	*%*
Uroporphyrin	0.4	<1.0	*%*
Erythrocytes porphyrins			
Total porphyrins	***28.0**	<1.9	*μmol/L RBC*
Erythrocyte UROS activity	***2.0**	>6.0	*U/mgHb/h*
Plasma porphyrins			
Total porphyrins	***1372**	<20	*nmol/L*
Fluorescence emission maximum peak	***620**	–	*nm*

Values in star are out of the normal range.

Figure 4. Congenital erythropoietic porphyria: discolouration of urine (2023).

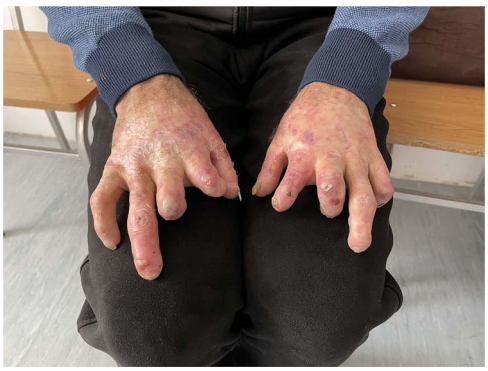

Figure 5. Amputation of the distal index and middle finger phalanges (2023).

to a deficiency of Uroporphyrinogen Decarboxylase (UROD) activity also inherited in an autosomal-recessive manner [5, 6]. In familial PCT, UROD activity is decreased in erythrocytes by

Figure 6. The destruction and deformation of the nose bridge nostrils (2023).

approximately 50% [7]. To date, bone marrow transplantation is the only curative therapy for CEP when an unrelated matched donor is available. It has been auspiciously carried out in some CEP patients, particularly children [8]. Genetically modified HSCT with a lentivirus-mediated vector in the murine CEP model showed complete and long-term correction of the disease; however, it has not yet been performed on humans [9]. Contemporary efforts to cure CEP concentrate on pharmacological approaches. New data have shown that molecular interaction may partially restore UROS stability and activity through modulation of protein folding, which paves the way for the elaboration of chaperone-based therapy [10].

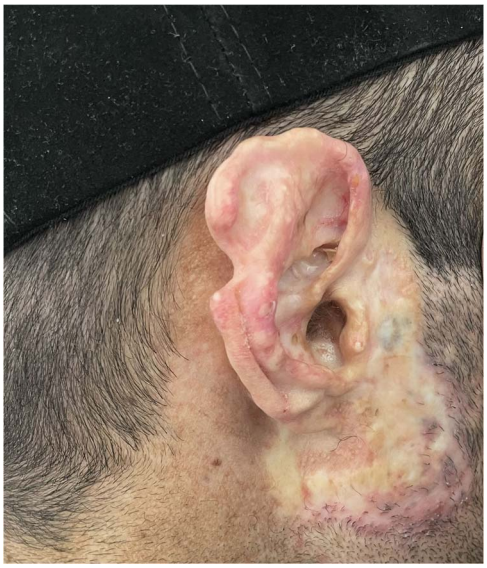

Figure 7. The destruction and deformation of auricles (2023).

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CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

None declared.

ETHICAL APPROVAL

This case report did not require review by the Ethics Committee.

CONSENT

Written informed consent was obtained from the patient to publish this case report and any accompanying images. A copy of the written permission is available for review by the Editor of this journal.

GUARANTOR

Marine Kamalyan.

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