Category of paper: Case Report

Article Title: Congenital erythropoietic porphyria

Running Title: Congenital erythropoietic porphyria

ABSTRACT

Congenital erythropoietic porphyria (CEP), or “Günther disease”, is a rare variant of porphyria. It is an autosomal recessive disease caused by deficient uroporphyrinogen III synthase (URO-III-synthase), the fourth enzyme in the heme biosynthetic pathway. We herein report a case of a man with the typical clinical presentations of hyper- and hypo-pigmentation and blister formation over sun-exposed areas, mutilation of the fingers, dark-purple urine, and erythrodontia with pinkish fluorescence under a Wood’s lamp. The diagnosis was confirmed by decreased activity of URO-III-synthase in red blood cells and a porphyrin profile compatible with CEP.

INTRODUCTION

Porphyrias are a diverse group of inherited or acquired heme biosynthesis disorders. Each sub-type results from deficient activity of a specific enzyme in the heme biosynthetic pathway. Congenital erythropoietic porphyria (CEP) is a rare sub-group with the most severe photosensitivity and mutilation.[1] Its typical features also include erythrodontia and dark-purple urine. The diagnosis is made by porphyria profile study and decreased relative enzyme activity. Here we present a male CEP patient with typical clinical presentations.

CASE REPORT

A 28-year-old male visited our dermatology department three years previously due to severe sun-burn after biking. A physical examination showed extreme scarring with multiple milia formation, dyspigmentation (Fig. 1A and 1B), and loss of acral tissues (mutilation of the fingers) (Fig. 1C and 1D) over frequently exposed skin areas (i.e., the face, forearms, hands and even shins). He also had brownish teeth (Fig. 2A and 2B), dark-purple urine (Fig. 2C and 2D), and icteric sclera emitting pinkish fluoresce under Wood's light detection. Porphyria was diagnosed, with consideration of congenital erythropoietic porphyria as the possible sub-type.

The patient had a healthy younger brother and no family history of porphyria and no consanguinity. After birth, he began to suffer from getting sunburned easily with noticeable blister formation on exposed areas, which required sun-protection. When he was one-year-old, the urine color changed gradually from red-purple to dark-purple. At that time, porphyria was already the impression but no further studies were performed. His teeth became brownish (erythrodontia) while he was in elementary school, and hypertrichosis developed with irregular hypo- and hyper-pigmentation over unprotected skin areas upon reaching puberty.

Since the high school years, he suffered from frequent malaise and anemia with hemoglobin fluctuating between 8 and 11 gm/dl. Eight years before visiting our

department, virus-associated hemophagocytic syndrome with pancytopenia caused his hemoglobin to drop from 10 to 3.5 gm/dl and he presented with severe weakness and headache, with splenomegaly proven by sonography. Furthermore, he suffered transfusion-dependent hemolytic anemia requiring monthly transfusions of 1000 ml of whole blood to maintaining Hb > 8 gm/dl 3 years before our first inspection. At this time his serum ferritin level was up to 6721 ng/ml.

On consultation, his porphyrin profile was analyzed through his stool and urine using high performance liquid chromatography and spectrofluorometry (Table 1). The urine study showed extremely increased levels of uroporphyrin isomer I and coproporphyrin isomer I, with a lesser degree of elevation in hepta-, hexa- and pentacarboxylporphyrin (7-, 6- and 5-COOH-porphyrin). The stool profile also reported extremely high levels of coproporphyrin I with an isomer III/I ratio of 0.1 and increased uroporphyrin I, although isomer III was almost undetectable. Moreover, the level of 5-COOH-porphyrin isomer III was much higher than isomer I, and despite no elevation in protoporphyrins, isocoproporphyrin was mildly elevated in the stool specimen. All of these findings were compatible with the clinical impression of CEP.

The activity of URO-III-synthase in red blood cells (RBC) was also evaluated by URO-III-synthase quasi coupled enzyme assay, and showed 15 relative units, much lower than the lower limit of 75 units of the reference range (Table 1). Given the

clinical presentation, porphyrin profile, and documented decrease in specific enzyme activity, CEP was the final diagnosis.

The patient did not accept transplantation due to fears of possible complications, and avoided sunlight as the only treatment.

DISCUSSION

Porphyrias are a group of disorders related to defects of enzymes processing the production of heme. Although traditionally categorized as hepatic or erythropoietic forms, they are also classified into dermatologic-dominant “non-acute” forms, in contrast to life-threatening “acute” forms that feature neurologic symptoms (Fig. 3) .[2]

Congenital erythropoietic porphyria is a very rare disease with only approximately 200 patients reported worldwide.[1,2] The first sign of CEP is often during the child’s first month, with pinkish or brown porphyrin staining of diapers. Severe photo-sensitivity and easy-blister formation after exposure to sunlight then develop in patients with severe forms. Recurrent wound formation with secondary bacterial infection may induce milia formation, disfigurement, and even auto-amputation (mutilation) over the digital tips, nose, or ears, while corneal scarring can lead to blindness.[3,4] CEP is the most mutilating type of the porphyrias, and squamous cell carcinomas over the distal ends have been reported with resorption.[5]

Large amounts of pathogenic porphyrins are excreted in stools and urine, which make the urine dark-purple with pinkish fluorescence. Similarly, red-brownish teeth with porphyrins also emit pinkish fluorescence under a Wood’s lamp (erythrodontia), which is a very special feature or even pathognomonic[2] of CEP. In the bones, fragility

and resorption of terminal phalanges may develop.[1,3,4,6]

Patients with the severe form will have marked hemolytic anemia and may be transfusion-dependent for life.[4] Secondary splenomegaly may also develop due to the increased uptake of abnormal erythrocytes and this, in turn, may exacerbate the anemia, leukopenia, and thrombocytopenia.[6,7]

In non-acute porphyria, both early onset CEP and erythropoietic protoporphyria are found, although CEP earlier than erythropoietic protoporphyria. Clinically, swelling erythema with minor blister formation is seen in erythropoietic protoporphyria, without pink-florescent urine. CEP may be similar with hepato-erythropoietic porphyria in mutilations, but without splenomegaly or elevated ferritin. [1,2,4,8] Porphyria cutaneous tarda is adult onset, which occurs without erythrodontia and a better prognosis than CEP.

URO-III-synthase normally catalyzes hydroxymethylbilane to uroporphyrinogen III, which is the real physiologic intermediate.[2,7] The deficient activity of URO-III-synthase directly leads to accumulated hydroxymethylbilane that is mostly non-enzymatically converted to uroporphyrinogen I. This is then catalyzed by uroporphyrinogen decarboxylase to form hepta-, hexa- and pentacarboxylporphyrinogen I, and ultimately, coproporphyrinogen I. This accumulates in the bone marrow (normoblasts and reticulocytes), erythrocytes,

plasma, bones, and teeth and undergo auto-oxidation to the corresponding porphyrins excreted in urine and stools. Since the next enzyme, coproporphyrinogen oxidase, is only specific to isomer III, coproporphyrinogen I is not catalyzed further.[7,9]

Our patient's urine and stool studies showed extremely increased levels of uroporphyrin and coproporphyrin, with lesser elevated hepta-, hexa- and pentacarboxyl porphyrins as in other case presentations. In addition, they were all isomer I dominant, although levels of isomer III were also increased.Extremely elevated levels of uroporphyrin isomer I and coproporphyrin isomer I with an obviously low ratio of isomer III/I in urine and stools are highly indicative of CEP.[2,7] In addition, the patient had very low URO-III-synthase activity (only 20% of the lower end of normal), which is different from uroporphyrinogen decarboxylase. This, together with the metabolite elevations and typical clinical presentations, made for a convincing argument for the diagnosis of CEP.[2,7,8,9]

Several papers have reported that cases with highly increased urinary porphyrin excretion usually have corresponding high concentrations in stools or plasma. [6,8] The most important finding in these reports was the high correlation between the severity of disease expression and the degree of porphyrin urinary excretion and porphyrin concentrations in stool and plasma, compatible with our patient.[10,11]

However, there was a very special finding in the porphyrin profile of our patient

- the moderately elevated level of isocoproporphyria in his stool - that may also indicate hepatoerythropoietic porphyria (HEP).[1,2] This is not typically seen in classic cases of CEP, and there were several findings that did not support the diagnosis of HEP. Clinically, this patient had a virtual pathognomonic picture of CEP, including erythrodontia and obvious serum iron concentration (ferritin 6721 ng/ml), which are not features of HEP.[2] Second, the extremely high coproporphyrin levels with a smaller increase of pentacarboxylporphyrin and undetectable hepta- and hexacarboxylporphyrin in his stool (and urine) all indicated normal function of uroporphyrinogen decarboxylase, the specifically defective enzyme in HEP.[2,7,12,13]

Chronic blood transfusion is effective for some patients by suppressing erythropoiesis then decreasing porphyrin formation, however iron overload is the really big problem, which was found in our patient.[14] Several other treatment modalities have been suggested in previous reports, such as, beta-carotene[15], oral charcoal [16,17], and splenectomy, however these were not performed on our patient. Stem cell transplantation, which was refused by our patient, is currently the only curative treatment, and several successful cases have been reported. [6,18,19,20]

In summary, we described the typical clinical and biochemical findings of CEP in a young Taiwanese male. In the past, most patients died by the age of 40 years, however improvements in supportive care (particularly use of antibiotics) have

improved the prognosis, though the hematological complications may be fatal.[21] Gene therapy by virus-mediated transfer of functional UROS cDNA into pathogenic hematopoietic stem cells has been reported in a mice model, with complete and long-term enzymatic, metabolic, and phenotypic correction. This may be an important curative methodology in the future.[22]

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Figures and Figure legends

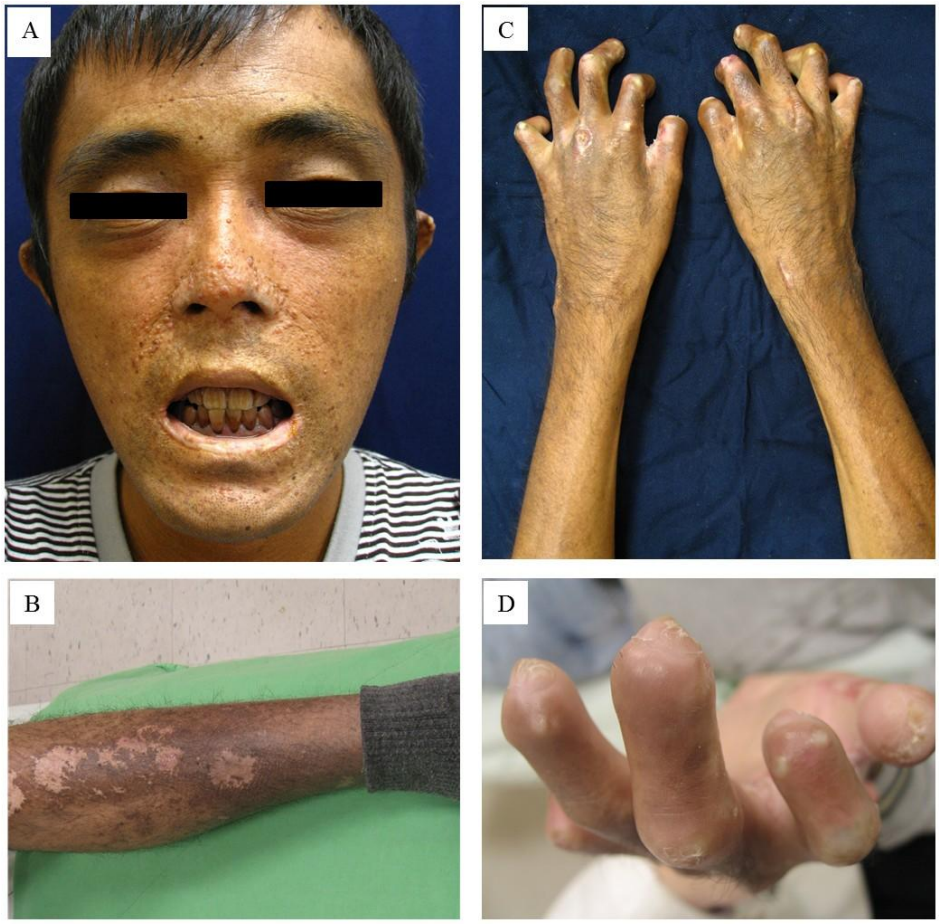

Fig. 1 A-D

Figure 1 **(A)** Multiple milia around the nose with icteric sclera and hyperpigmented face. **(B)** Obvious dyspigmentation over the shin. **(C)** Severe mutilation of the fingers with scarring and hypertrichosis over sun-exposed areas. **(D)** Close-up view of the mutilation of the fingers.

Fig. 2 A-D

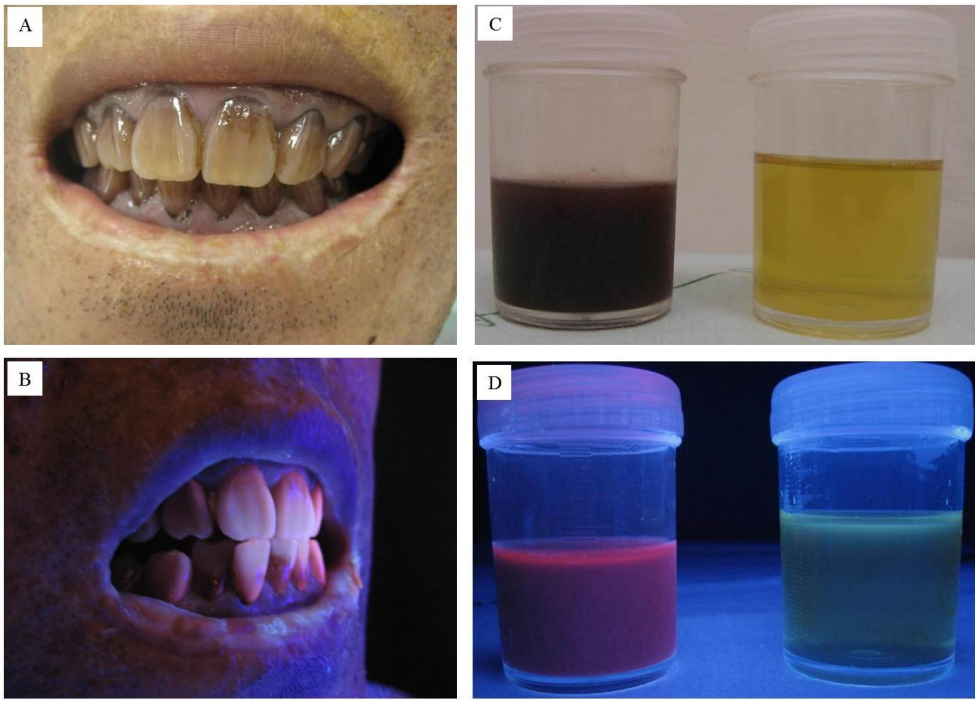

Figure 2 **(A)** Brownish teeth with **(B)** pinkish fluorescence under Wood's light detection. **(C)** The dark-purple urine of our patient (left) compared with a normal person's light-yellow urine (right). **(D)** Pinkish fluorescence under Wood's light detection (left) compared with the normal sample (right).

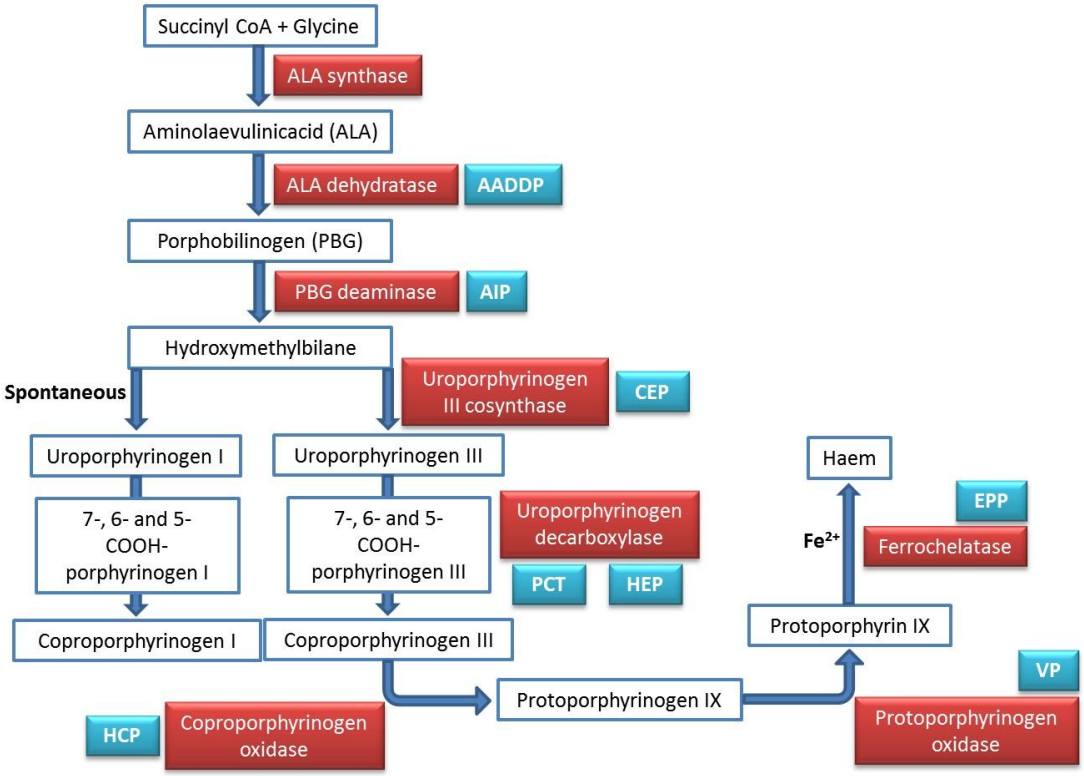

Figure 3 The pathway of haem biosynthesis

The red boxes represent enzymes, and the blue boxes indicate the relative porphyria subtypes.7-, 6- and 5-COOH-porphyrinogen mean hepta-, hexa- and pentacarboxylporphyrin respectively.

Acute form includes AADDP, AIP, VP and HCP, while non-Acute form includes PCT, EEP, CEP and HEP

AADDP:δ -Aminolevulinic Acid Dehydratase Deficiency Porphyria

AIP: Acute Intermittent Porphyria

CEP: Congenital Erythropoietic Porphyria

PCT: Porphyria Cutanea Tarda

HEP: Hepatoerythropoietic Porphyria

HCP: Hereditary Coproporphyria

VP: Variegate Porphyria

EPP: Erythropoietic Protoporphyria

Table 1 Porphyrin profiles reports in urine and stool specimens & Uroporphyrinogen III Synthase activity in RBC

Urine				**Stool**			
Porphyrins		RR	Elevated	Porphyrins		RR	Elevated
Uroporphyrin	245345 *	<30	yes	Uroporphyrin I	942 ‡	<120	yes
Heptacarboxylporphyrin	13284 *	<9	yes	Uroporphyrin III	<1 ‡	<50	
Hexacarboxylporphyrin	4482 *	<8	yes	Heptacarboxylporphyrin I	<1 ‡	<40	
Pentacarboxylporphyrin	11538 *	<10	yes	Heptacarboxylporphyrin III	<1 ‡	<40	
Coproporphyrin	50907 *	<230	yes	Isoheptacarboxylporphyrin	<1 ‡	<30	
Porphobilinogen	1.5 †	<2.2		Hexacarboxylporphyrin I	<1 ‡	<10	
				Hexacarboxylporphyrin III	<1 ‡	<10	
				Isohexacarboxylporphyrin	523 ‡	<10	yes
				Pentacarboxylporphyrin I	3726 ‡	<20	yes
				Pentacarboxylporphyrin III	204 ‡	<20	yes
				Isopentacarboxylporphyrin	875 ‡	<80	yes

				Coproporphyrin I	310608 ‡	<500	yes
				Coproporphyrin III	32294 ‡	<400	yes
				Isocoproporphyrin	1640 ‡	<200	yes
				Protoporphyrin	329 ‡	<1500	
				Coproporphyrin I/III ratio	**0.1**		
Uroporphyrinogen III Synthase relative activity, RBC							
Relative unit : 15 §				Reference range : >75			

RR : Reference range

Units: * Nanomoles/24 hours, † Micromoles/24 hours, ‡ Micrograms/24 hours

§ : The proportion of series III isomers formed in relation to total porphyrins (I + III isomers) represents the relative activity of Uroporphyrinogen III Synthase.