Late-onset hepatoerythropoietic porphyria presenting with facial deformities and erythrodontia

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ABSTRACT :

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Hepatoerythropoietic porphyria (HEP) is a nonacute porphyria inherited as an autosomal recessive disorder due to either a homozygous or compound heterozygous deficiency of uroporphyrinogen decarboxylase (UROD). The incidence of HEP is extremely rare, with fewer than 40 cases reported to date. The typical onset is in early childhood, and it usually presents with severe photosensitivity, mutilating scarring, and hypertrichosis. We report a 48-year-old man with teenage onset (15 years of age) of HEP.

Key words: Hepatoerythropoietic porphyria, facial deformities, erythrodontia, late-onset

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Introduction

Porphyrias result from inherited and acquired dysfunctions of enzymes crucial for heme biosynthesis. They are classified into nonacute and acute porphyrias. Hepatoerythropoietic porphyria (HEP) is a nonacute porphyria inherited as an autosomal recessive disorder due to either a homozygous or compound heterozygous deficiency of uroporphyrinogen decarboxylase (UROD).[1] The incidence of HEP is extremely rare, with fewer than 40 cases having been reported to date.[1] Clinical onset typically occurs in early childhood (< 4 years) and usually presents with severe photosensitivity, mutilating scars, and hypertrichosis.[1] The authors describe a 48-year-old man with teenage onset of HEP.

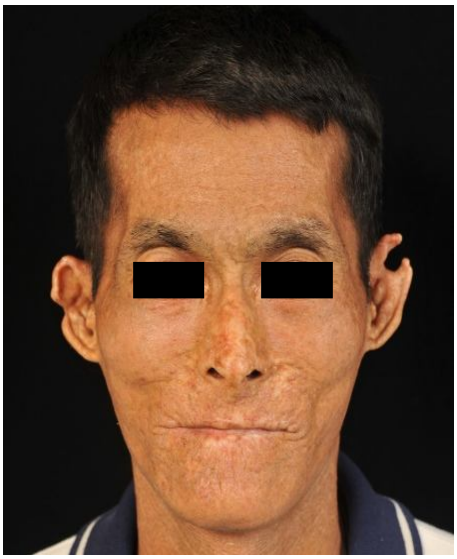

Figure 1 Bird-beak facial appearance, bilateral ear helix deformities, perioral furrow

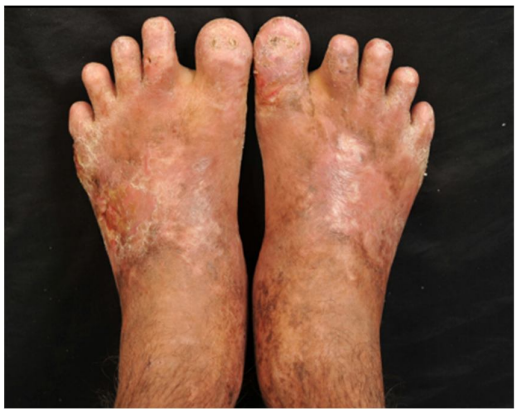

Figure 2 Resorption and shortening of toes

Case report

A 48-year-old Thai male from Kanchanaburi Province, Thailand, presented with multiple vesicles and blisters on his face, both hands, and the dorsum of feet, with symptoms first appearing when he was 15 years old. The lesions had been aggravated by sunlight and had resolved with scars. At the age of 20, the lesions gradually progressed to deformities on both hands and feet. Thereafter, he developed sclerodermoid changes on his face and neck, with progressively limited mouth opening and hypertrichosis on his back and chest wall. His teeth became brownish. He denied any history of dysphagia and dyspnea. He did not take alcohol or systemic medications. Two months before the dermatologist consultation, he had begun to gradually develop blurred vision in both eyes and was diagnosed as having bilateral necrotizing scleritis by an ophthalmologist. No

history of acute porphyria attacks, such as abdominal pain, vomiting, neurological, or psychiatric symptoms, was reported. Similar skin conditions were noted in one of the patient's eight siblings.

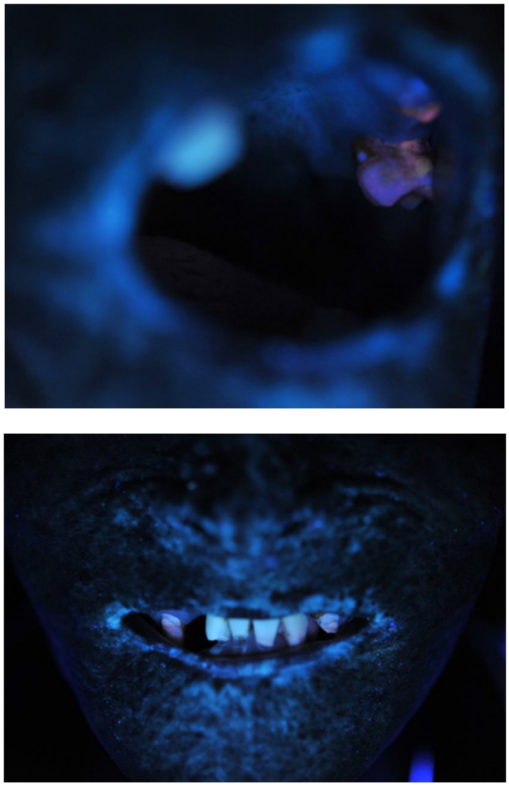

Figure 3 Erythrodontia under Wood's lamp examination

A physical examination revealed a bird-beak facial appearance, bilateral ear helix deformities, and perioral furrowing (Figure 1). He had a sclerodermoid skin change with hypo- and hyperpigmentation on the face, neck, extremities, hands, and feet (Figure 2). Hypertrichosis was noted on his back, chest wall, and both legs. He also developed fixed flexion deformities, and resorption and shortening of the tips and toes of all fingers (Figure 2). Anonychia was seen in all of his fingernails and toenails. His teeth were observed to have a brown discoloration with red fluorescence (erythrodontia) under a Wood' light examination (Figure 3).

Laboratory findings showed a normal complete blood count and normal liver function test results. The viral hepatitis profiles (HBsAg and anti-HCV) were negative. Pink-red urine was apparent under a Wood's lamp examination. The urine porphyrin quantitative findings with normal Thai subjects reference ranges[2] are as shown in Table 2 and consistent with those found in porphyria cutanea tarda or hepatoerythropoietic porphyria (see discussion). The fluorescence emission scan of the patient's plasma showed the emission peak at 618 nm. The preliminary results of the erythrocyte protoporphyrin quantification showed that zinc protoporphyrin was predominantly and significantly elevated, compared with those from the normal subjects.[3] Based on the clinical evidence of severe photosensitivity, erythrodontia, markedly increased levels of uroporphyrin versus coproporphyrin, a peak plasma fluorescent at 618 nm, and the increased

levels of zinc protoporphyrin in the RBC, HEP should be the final diagnosis. UROD gene detection was not available at our institution. Appropriate photoprotection by sunscreen and clothing were advised to the patient.

Table 1 Late-onset hepatoerythropoietic porphyria cases

Authors	Gender	Age (Year)	Age onset (Year)	Cutaneous manifestations	Systemic symptoms
Cantatore-Francis JL, et al.[6]	Female	7	7	Acute photosensitivity, erosions, linear to polygonal scar sclerodactyly, milia, mottled hyperpigmentation, facial hypertrichosis, brownish teeth, small nose with depressed bridge	Reddish urine hemolytic anemia, neonatal thrombocytopenia, developmental delay, abnormal gait, polyarticular arthritis
Remenyik E´, et al.[10]	1.Male	9	9	Hyperpigmentation, facial hypertrichosis, superficial scars on dorsal of hands	N/A
	2.Male	16	16		
	3.Female	19	19		
Armstrong DK, et al.[11]	Male	38	13	Skin fragility, bullae and scar on dorsal of hands	N/A
Moran-Jimenez MJ, et al.[4]	Female	30	30	Cutaneous symptoms after the administration of estrogens and iron	N/A
Horina JH, et al.[12]	Male	68	36	Disfiguring scar with inflamed erosions on sun-exposed area	Severe heart failure
This study	Male	48	15	Vesicles, bullae, scar, sclerodermoid skin change on sun-exposed areas, ear, hands and feet deformity, hypertrichosis, erythrodontia	N/A

N/A, not applicable

Table 2 Laboratory findings of late-onset hepatoerythropoietic porphyria cases

	Cantatore-Francis JL et al.6	Remenyik et al.[10]			Armstrong et al.[11]	Moran-Jimenez et al.[4]	Horina et al.[12]	This study* (reference range)
		Case 1	Case 2	Case 3				
Urine								
Total porphyrin	↑↑	↑↑	↑↑	↑	↑↑	N/A	N/A	N/A
Uroporphyrinogen	↑	↑	↑	↑	↑	N/A	↑↑	1170.5 (0.2 - 2.7) ↑↑↑
Uroporphyrinogen intermediates	↑	↑↑	↑↑	↑↑	↑	N/A	↑↑	44.3 (0 - 0.2) ↑↑
- Heptacarboxyl porphyrin	↑	↑	↑	↑	↑	N/A	N/A	22.6 (0 - 0.1) ↑↑
- Hexacarboxyl porphyrin	↑	↑	↑	↑	↑↑	N/A	N/A	93.8 (0 - 0.3) ↑↑
- Pentacarboxyl porphyrin								
Coproporphyrin								
- Total	N/A	N/A	↓	↓	↓↓	N/A	N/A	598.7 (3.1 - 34.9) ↑↑
- Isomer I	N/A	N/A	N/A	N/A	N/A	N/A	N/A	593.7 (1.0 - 13.5) ↑↑
- Isomer III	N/A	N/A	N/A	N/A	N/A	N/A	N/A	5.0 (1.7 - 23.6)
- Isomer III/I ratio	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.01 (0.52 – 2.95) ↓↓
- Uro-/ Coproporphyrin ratio	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1.96 (0.03 - 0.15) ↑↑
Plasma								
Total porphyrin	↑↑	↑↑	↑↑	↑↑	N/A	N/A	N/A	N/A
Peak plasma fluorescence	619	N/A	N/A	N/A	N/A	N/A	N/A	618
(nm)	↑↑	N/A	N/A	N/A	N/A	N/A	N/A	↑
Erythrocyte protoporphyrin level	N/A	N/A	N/A	N/A	↑	N/A	N/A	↑
Zinc protoporphyrin								
Stool								
Total porphyrin	N/A	↑	N/A	↑	↑	N/A	N/A	N/A
Isocoproporphyrin	N/A	N/A	N/A	N/A	↑	N/A	↑	N/A
5CO_2H-porphyrin	N/A	N/A	N/A	N/A	↑	N/A	N/A	N/A
Dicarboxylic porphyrins	N/A	N/A	N/A	N/A	↑	N/A	N/A	N/A
Coproporphyrin	N/A	N/A	N/A	N/A	↑	N/A	↑	N/A
Coproporphyrin isomer III / I ratio	N/A	N/A	N/A	N/A	↑	N/A	N/A	N/A

Table 2 Laboratory findings of late-onset hepatoerythropoietic porphyria cases

	Cantatore-Francis JL et al.6	Remenyik et al.[10]			Armstrong et al.[11]	Moran-Jimenez et al.[4]	Horina et al.[12]	This study* (reference range)
		Case 1	Case 2	Case 3				
UROD enzyme activity	N/A	42 %	47.5	44 %	< 5%	70 %	16%	N/A
UROD mutation	645del1053/ins10 V166A	(100) M1V/P23	%(100) M1V/P23	(100) M1V/P23	Absent	Y311C	N/A	N/A
HFE mutation	H63D	5S	5S	5S	H63D, C282Y		N/A	N/A
		N/A	N/A	N/A	N/A			

↑↑, markedly increased; ↑, increased; ↓, decreased; N/A, not applicable; UROD, uroporphyrinogen decarboxylase; HFE, human factors engineering

* Urinary porphyrin concentrations were determined from a random urine specimen of the patient and expressed as μmol/mol creatinine. The porphyrin quantification methods and the reference ranges in normal Thai subjects are as reported by Peerapittayamongkol et al.[2]

Discussion

Hepatoerythropoietic porphyria (HEP) is inherited as an autosomal recessive disorder due to either a homozygous or compound heterozygous deficiency of uroporphyrinogen decarboxylase (UROD), which is the 5th enzyme of the heme-biosynthetic pathway.[1,4] Deficiency of UROD can be seen in HEP and porphyria cutanea tarda (PCT). The clinical manifestations of both HEP and PCT are severe cutaneous photosensitivity with bullae prominent on sun-exposed areas, scarring, sclerodermoid skin changes, hyperpigmentation, and hypertrichosis, but mutilation is most often seen in HEP.[4] HEP is often detected in early childhood and improves with age[4], whereas PCT is unusual before puberty, typically being diagnosed in the third and fourth decades of life.[1] Most HEP and PCT patients present with dark-red urine. Erythrodontia is caused by the accumulation of porphyrin in the teeth, which can be seen in HEP and congenital erythropoietic porphyria (CEP).[5, 6] Pink-red urine under a Wood's lamp examination can be found in PCT, HEP, CEP, and variegate porphyria (VP).[4] However, a peak plasma fluorescence at 618 nm is consistent with HEP, PCT, or CEP. Therefore, VP can be excluded. From the uroporphyrin to coproporphyrin ratio of 1.96, CEP can be excluded because CEP has an elevation of coproporphyrin rather than uroporphyrin. In HEP and PCT, this ratio is usually more than 1, which indicates a higher elevation of uroporphyrin than coproporphyrin. Another biochemical feature of HEP and PCT is the elevation of uroporphyrinogen intermediates (i.e., hepta-, hexa-, pentacarboxyl porphyrins)

resulting from the defect of the stepwise decarboxylation of uroporphyrinogen III due to UROD deficiency. This enzymatic defect also leads to the elevation of coproporphyrin-isomer I through the non-enzymatic production of uroporphyrinogen I. Importantly, HEP displays a marked increase in erythrocyte zinc protoporphyrin[7], which is formed from intermediate porphyrins metabolized to protoporphyrin and complexed with zinc[8,9]; by contrast, the erythrocyte zinc protoporphyrin level in PCT is normal because abnormal heme biosynthesis occurs in the liver. From the clinical presentation and the biochemical markers of noticeably increased levels of uroporphyrin rather than coproporphyrin, the peak plasma fluorescent at 618 nm, and the increased levels of RBC zinc protoporphyrin, HEP was diagnosed. Even though UROD gene mutation detection was not performed for this patient, the diagnosis of HEP can be made from the biochemical features.

Most patients develop HEP in early childhood (< 4 years). However, the present patient started to develop the symptoms of HEP from the age of 15, which can be implied as late-onset HEP. Some reported cases of late-onset HEP have had mild symptoms.[4] To date, 7 cases of late-onset HEP (≥7 years) have been reported with different degrees of systemic involvement (Table 1[4,6,10-12] and Table 2[2,4,6,10-12]). Photoprotection is the mainstay treatment for HEP; no other effective treatments have been reported.[4]

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