Two Brothers With Mild Congenital Erythropoietic Porphyria Due to a Novel Genotype

Ali A. Berry, MD; Robert J. Desnick, MD, PhD; Kenneth H. Astrin, PhD; Junard Shabbbeer, PhD; Anne W. Lucky, MD; Henry W. Lim, MD

Background: Congenital erythropoietic porphyria (CEP) is a rare autosomal recessive disease caused by the deficient activity of the heme biosynthetic enzyme, uroporphyrinogen III synthase (URO-synthase), and the accumulation of the nonphysiologic and phototoxic porphyrin I isomers. Clinical manifestations range from severe mutilation to mild erosions and blisters on sun-exposed areas. Evaluation of the URO-synthase mutation and residual enzyme activity has been correlated with the phenotypic expression of the disease.

Observations: We describe 16- and 4-year-old brothers with CEP with a mild phenotype due to a novel genotype, one allele having a promoter mutation (−76G→A) and the other having an exonic missense mutation (G225S). The father and a 4-year-old fraternal twin brother were carriers of the −76G→A mutation, whereas the mother and a 15-year-old brother were carriers of the G225S mutation. Previous in vitro expression studies demonstrated that the G225S mutation severely decreased URO-synthase activity to 1.2% of normal, whereas the promoter mutation decreased the activity to approximately 50% of wild type, accounting for the mild clinical phenotype.

Conclusion: The mild disease phenotype in these patients is a further example of the clinical heterogeneity seen in CEP and is additional proof that in vitro enzyme expression studies provide dependable genotype-phenotype correlations.

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ception of the severe C73R missense mutation, which occurred in nearly 30% of the disease alleles.\(^3,8\) In vitro studies\(^3\) that characterized the residual URO-synthase enzymatic activity expressed by different mutations revealed that the level of residual activity directly correlated with the disease severity; namely, higher residual URO-synthase activity levels resulted in milder CEP phenotypes, and lower residual enzymatic activity levels resulted in a more severe phenotype.

In this article, we describe 2 brothers who have a mild CEP phenotype and a previously unreported genotype, −76G→A/G225S. The mild phenotype in our patients further supports previous work indicating a strong genotype-phenotype correlation in this disease. Although the residual URO-synthase activity expressed by the severe G225S missense exonic mutation was only 1.2% of normal,\(^9\) the residual enzyme activity associated with −76G→A promoter substitution was 54% of mean activity expressed by the normal allele in vitro, substantially higher than that seen in severe cases.\(^3,10\)

### REPORT OF CASES

#### CASE 1

A 16-year-old white adolescent boy was referred to the Department of Dermatology, Henry Ford Hospital, Detroit, Mich, for skin fragility, blister formation, and mild scarring of the face, arms, and legs since age 3 years. He reported having mild cutaneous photosensitivity and frequent reddish discoloration of the urine. Occasional splenomegaly had been detected, but no frank episodes of hemolysis had occurred. He had been evaluated for occasional abdominal pain, but no cause was found. No joint pains or neuropsychiatric symptoms were reported. His younger brother had a similar condition (see case 2), whereas his parents and other siblings had no symptoms of photosensitivity or any cutaneous findings.

Physical examination showed hypertrichosis over the periorbital area (Figure 1), several shallow scars on the forehead, and scattered crusted erosions with mild non-mutilating scarring over the dorsum of the hands (Figure 2) and extensor surfaces of the forearms. There was no hepatosplenomegaly.

On the basis of these findings, cutaneous porphyria was suspected, and the patient’s plasma, erythrocyte, urine, and fecal porphyrin levels and erythrocyte uroporphyrinogen decarboxylase activity were evaluated. The results were consistent with the diagnosis of CEP because a marked increase in total urinary, plasma, erythrocyte, and fecal porphyrin levels was detected, with a predominance of URO-I and COPRO-I isomers in the urine and plasma and COPRO-I in the stool (Table). Uroporphyrinogen decarboxylase activity was normal, thus excluding the diagnosis of porphyria cutanea tarda or hepatoerythropoietic porphyria. Analysis of genomic DNA revealed a novel combination of mutant URO-synthase alleles, a paternally inherited promoter mutation (−76G→A) and maternally inherited missense exonic mutation (G225S).\(^9,11\)

#### CASE 2

The 4-year-old brother of the patient in case 1 was referred to the Department of Dermatology, Henry Ford Hospital, complaining of pruritic and painful erosions and blistering with mild scarring on sun-exposed skin since 18 months of age. He was the product of a full-term pregnancy and uncomplicated delivery. He was born healthy and had not had any hemolysis or organomegaly. He had had no abdominal or joint pains. With a notable exception of his 16-year-old brother (case 1), his parents and...
2 other siblings, including a fraternal twin, did not have any similar complaints.

Physical examination revealed crusted erosions on the nasal bridge and forehead (Figure 3). Erosions, superficial scars, hyperpigmentation, and milia were observed on the nape of the neck, dorsum of the hands (Figure 4), and extensor extremities. Hypertrichosis was noted on the face, forearms, and legs; no lesions were noted in the non–sun-exposed areas. There was no hepatosplenomegaly.

Similar to case 1, cutaneous porphyria was suspected and the patient’s plasma, erythrocyte, urine, and fecal porphyrin levels and erythrocyte uroporphyrinogen decarboxylase activity were evaluated. The results were consistent with a diagnosis of CEP; a marked increase in total urinary, plasma, erythrocyte, and fecal porphyrin levels was detected with a predominance of URO-I and COPRO-I isomers in the urine and plasma and COPRO-I in the stool (Table). Erythrocyte uroporphyrinogen decarboxylase activity was normal. As shown in Figure 5, genetic testing further supported the diagnosis of CEP because the −76G→A/G225S genotype was identified.

**STUDIES OF FAMILY MEMBERS**

The results of mutation detection studies of all family members are shown in Figure 5. One of the father's URO-

<table>
<thead>
<tr>
<th>Porphyrin Precursors and Porphyrins</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>5'-Aminolevulinic acid in urine, mg/24 h</td>
<td>2.5</td>
<td>0.9</td>
<td>0-7</td>
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<tr>
<td>Porphobilinogen in urine, mg/24 h</td>
<td>0.7</td>
<td>0.2</td>
<td>0-4</td>
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<tr>
<td>Total porphyrins in urine, nmol/24 h</td>
<td>8073</td>
<td>3590</td>
<td>0-300</td>
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<td>Porphyrin pattern, nmol/L (I/III isomer ratio)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uroporphyrin</td>
<td>6135 (98)</td>
<td>22,764 (98)</td>
<td>0-90</td>
</tr>
<tr>
<td>Coproporphyrin</td>
<td>1049 (98)</td>
<td>503 (98)</td>
<td>150-300</td>
</tr>
<tr>
<td>Heptacarboxyl porphyrin</td>
<td>242</td>
<td>72</td>
<td>0-15</td>
</tr>
<tr>
<td>Hexacarboxyl porphyrin</td>
<td>161</td>
<td>36</td>
<td>0-15</td>
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<tr>
<td>Pentacarboxyl porphyrin</td>
<td>484</td>
<td>215</td>
<td>0-15</td>
</tr>
<tr>
<td>Isocoproporphyrin</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total plasma porphyrin, µg/dL</td>
<td>12.3</td>
<td>8.6</td>
<td>0-0.9</td>
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<tr>
<td>Protoporphyrin in erythrocytes, µg/dL</td>
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<td>376</td>
<td>0</td>
</tr>
<tr>
<td>Hematocrit in erythrocytes, %</td>
<td>43.6</td>
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<tr>
<td>Total porphyrin in feces, nmol/g dry weight</td>
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<td>836</td>
<td>0-200</td>
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<tr>
<td>Porphyrin pattern, nmol/g dry weight (I/III isomer ratio)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Uroporphyrin</td>
<td>0</td>
<td>0</td>
<td>0-20</td>
</tr>
<tr>
<td>Coproporphyrin</td>
<td>1370 (98)</td>
<td>803 (98)</td>
<td>60-200</td>
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<tr>
<td>Pentacarboxyl porphyrin</td>
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<td>25</td>
<td>0-20</td>
</tr>
<tr>
<td>Protoporphyrin</td>
<td>0</td>
<td>1</td>
<td>60-200</td>
</tr>
</tbody>
</table>

*Porphyrin analyses performed by Karl E. Anderson, MD, University of Texas Medical Branch, Galveston.

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**Figure 3.** Erosions and crusting on the forehead in case 2. Note hypertrichosis on the temple.

**Figure 4.** Crusted erosions, milia, and postinflammatory hyperpigmentation on the dorsum of the hand in case 2. Note a small vesicle on the lateral aspect of the index finger.

**Figure 5.** Pedigree showing genotype and phenotype of patients and their family. WT indicates wild type; black squares, affected individuals; half black squares and circle, carrier individuals; squares, male; and circle, female.
synthase alleles had the −76G→A promoter mutation, and one of the mother’s URO-synthase alleles contained the G225S missense mutation. A 15-year-old male sibling of the affected brothers carried the G225S mutation, whereas the 4-year-old fraternal twin brother of the patient in case 2 carried the promoter mutation. Except for the 2 affected siblings, none of the family members had any signs or symptoms of CEP.

**TREATMENT**

Both patients were advised to avoid sun exposure and to use inorganic sunscreens that contained zinc oxide or titanium dioxide. They were also provided with inorganic sunscreen formulated as a paste with coloring that could be matched to skin color.12 This was more acceptable and practical for use. The patients and their family members also received genetic counseling. They subsequently reported better control of their cutaneous eruptions. Except for limiting sun exposure, the affected brothers have been able to lead normal lives.

**COMMENT**

Congenital erythropoietic porphyria is an inborn error of heme biosynthesis that results from the markedly deficient, but not absent, activity of URO-synthase and the resulting accumulation of uroporphyrinogen I and coproporphyrinogen I, which are oxidized to the nonphysiologic porphyrin 1 isomers, URO-I and COPRO-I.1-3 Light in the Soret region band (400-410 nm) activates the phototoxic URO-I and COPRO-I isomers, resulting in skin fragility, blisters, milia, and mutilating scars. Other clinical manifestations include erythroderma, alopecia, and hypertrichosis. Patients with severe CEP present with mutilating cutaneous involvement starting in the neonatal period, are transfusion dependent, and have hypersplenism. Patients with late-onset disease usually present with only mild cutaneous lesions5,5 and may develop thrombocytopenia and myelodysplasia.5,13,14; they are not transfusion dependent. On the basis of the in vitro expression of the individual mutant alleles found in cases of CEP, it has been shown that the residual URO-synthase activity in milder cases is higher than the residual URO-synthase activity in severe cases.3,15,16

To date, more than 35 URO-synthase mutations are listed in the Human Gene Mutation Database.3,7 Patients have been described who are homoallelic or heteroallelic for different mutations. For example, the most common mutation, C73R, has occurred in severely affected individuals when homoallelic (C73R/C73R) and in moderately affected patients when heteroallelic (C73R/A104V).3 Thus, the genotype is directly correlated with the amount of expressed URO-synthase activity, as previously shown by in vitro studies, and is also directly correlated with disease severity.3,9,10 In our patients, the novel genotype consisted of 2 different mutations, a promoter region point mutation (−76G→A) in one allele and an exonic missense mutation (G225S) in the other. Previous in vitro expression of the −76G→A allele and the G225S allele in *Escherichia coli* revealed residual URO-synthase activities of 53.9% and 1.2%, respectively, of the mean in vitro wild-type expressed activity.9,10 This suggests that the mild phenotype seen in our patients is due to the compensatory residual activity of the URO-synthase activity produced primarily by the −76G→A allele. The delay in onset of disease in our patients (3 years of age in case 1 and 18 months of age in case 2) may be due to the slow rate of accumulation of the porphyrin isomers in reaching a threshold pathogenic level. A similar phenomenon has been postulated for patients with myelodysplastic disease who develop late-onset CEP, which is usually mild.5,13,14

The management of the cutaneous manifestations of CEP consists of strict sun avoidance, use of inorganic sunscreens, and prompt treatment of secondary bacterial skin infections. Inorganic sunscreens that contain zinc oxide or titanium dioxide are best if applied as a paste, but this may be impractical and cosmetically unappealing for most patients. Other treatment modalities with limited efficacy include oral beta carotene, intravenous hematin, plasmapheresis, hydroxychloroquine, oral charcoal, and other porphyrin binders.2,17 For severely affected patients who are transfusion dependent, erythrocyte transfusion,19 hydroxyurea,19 and splenectomy20 appear effective, at least until adolescence; stem cell or bone marrow transplantation has been curative.20,21 In vitro gene transfer studies have demonstrated restoration of URO-synthase activity, suggesting the future potential effectiveness of gene therapy.22,24

In summary, we describe 2 brothers with CEP who have an unusually mild phenotype due to a novel heterozygous genotype that consists of a promoter mutation (−76G→A) and an exonic missense mutation (G225S). The mild disease in these patients is a further example of the clinical heterogeneity seen in CEP and is additional proof that in vitro enzyme expression studies can correlate genotype to phenotype.

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**Author Contributions:** Study concept and design: Berry, Desnick, and Lim. Acquisition of data: Berry, Desnick, Astrin, Shabbeer, Lucky, and Lim. Analysis and interpretation of data: Desnick, Lucky, and Lim. Drafting of the manuscript: Berry, Desnick, and Lim. Critical revision of the manuscript for important intellectual content: Berry, Desnick, Astrin, Shabbeer, Lucky, and Lim. Obtained funding: Desnick. Administrative, technical, and material support: Berry, Desnick, Shabbeer, and Lim. Study supervision: Desnick, Astrin, and Lim.

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