CASE REPORT

Congenital erythropoietic porphyria

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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 (RBC) 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 Typical features of CEP also include erythrodontia and dark-purple urine. The diagnosis is made by porphyrin 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 3 years previously due to severe sun-burn after hiking. A physical examination showed extreme scarring with multiple milia formation, dyspigmentation (Figures 1A and 1B), and loss of acral tissues (mutilation of the fingers) (Figures 1C and 1D) over frequently exposed skin areas (i.e., the face, forearms, hands and shins). He also had brownish teeth (Figures 2A and 2B), dark-purple urine (Figures 2C and 2D), and icteric sclera emitting pinkish fluorescence under Wood’s lamp. Porphyria was diagnosed, with decreased activity of URO-III-synthase in red blood cells (RBC) and a porphyrin profile compatible with CEP. Since his high school years, the patient suffered from frequent malaise and anemia with hemoglobin fluctuating between 8 and 11 g/dL. Eight years before visiting our department, virus-associated hemophagocytic syndrome with pancytopenia caused his hemoglobin to drop from 10 to 3.5 g/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 maintain Hb > 8 g/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 showed 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.

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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 (Figure 3).2

CEP is a very rare disease with only approximately 200 patients reported worldwide.1,2 The first sign of CEP is often during a child’s 1st 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 pathognomonic2 of CEP. In the bones, fragility and resorption of terminal phalanges may develop.1,3,4

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 is found 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 hepatoerythropoietic porphyria in mutilations, but without splenomegaly or elevated ferritin.1,2,4,8 Porphyria cutanea tarda is adult onset, occurs without erythrodontia, and has 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
isomers) represents the relative activity of uroporphyrinogen III synthase. RR: Reference range.

Table 1 Porphyrin profile reports in urine and stool specimens and uroporphyrinogen III synthase activity in RBC.

<table>
<thead>
<tr>
<th>Porphyrins</th>
<th>RR</th>
<th>Elevated</th>
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</thead>
<tbody>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uroporphyrin (nmol/24 h)</td>
<td>245345</td>
<td>&lt;30</td>
</tr>
<tr>
<td>Heptacarboxylporphyrin (nmol/24 h)</td>
<td>13284</td>
<td>&lt;9</td>
</tr>
<tr>
<td>Hexacarboxylporphyrin (nmol/24 h)</td>
<td>4482</td>
<td>&lt;8</td>
</tr>
<tr>
<td>Pentacarboxylporphyrin (nmol/24 h)</td>
<td>11538</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Coproporphyrin (nmol/24 h)</td>
<td>50907</td>
<td>&lt;230</td>
</tr>
<tr>
<td>Porphobilinogen (nmol/24 h)</td>
<td>1.5</td>
<td>&lt;2.2</td>
</tr>
<tr>
<td><strong>Stool</strong></td>
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<tr>
<td>Uroporphyrin I (µg/24 h)</td>
<td>942</td>
<td>&lt;120</td>
</tr>
<tr>
<td>Uroporphyrin III (µg/24 h)</td>
<td>&lt;1</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Heptacarboxylporphyrin I (µg/24 h)</td>
<td>&lt;1</td>
<td>&lt;40</td>
</tr>
<tr>
<td>Heptacarboxylporphyrin III (µg/24 h)</td>
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<td>&lt;40</td>
</tr>
<tr>
<td>Isoheptacarboxylporphyrin (µg/24 h)</td>
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<td>&lt;30</td>
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<td>&lt;10</td>
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<td>Isohexacarboxylporphyrin (µg/24 h)</td>
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<td>Isopentacarboxylporphyrin (µg/24 h)</td>
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<td>Coproporphyrin I (µg/24 h)</td>
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<tr>
<td>Coproporphyrin III (µg/24 h)</td>
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</tr>
<tr>
<td>Isocoproporphyrin (µg/24 h)</td>
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<td>&lt;200</td>
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<tr>
<td>Protoporphyrin (µg/24 h)</td>
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<td>&lt;1500</td>
</tr>
<tr>
<td>Coproporphyrin I/III ratio</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

Uroporphyrinogen III synthase relative activity, RBC

Relative unit: 15a Reference range: >75

RR: Reference range.

* The proportion of series III isomers formed in relation to total porphyrins (I + III isomers) represents the relative activity of uroporphyrinogen III synthase.

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).

Uroporphyrinogen decarboxylase to form hepta-, hexa- and pentacarboxylporphyrinogen I, and ultimately, coproporphyrinogen I. This accumulates in the bone marrow (normoblasts and reticuloocytes), erythrocytes, plasma, bones, and teeth and undergoes 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.

The urine and stool studies of our patient 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. 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.

Several papers have reported that cases with highly increased urinary porphyrin excretion usually have corresponding high concentrations in stools or plasma. 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.

However, there was a very special finding in the porphyrin profile of our patient — the moderately elevated level of isocoproporphyrin in his stool — that may also indicate hepatoerythropoietic porphyria (HEP). 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 erythrodoncia and obvious serum iron concentration (ferritin 6721 ng/mL), which are not features of HEP. Secondly, 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.
Chronic blood transfusion is effective for some patients by suppressing erythropoiesis and then decreasing porphyrin formation, however, iron overload is the really big problem, which was found in our patient. Several other treatment modalities have been suggested in previous reports, such as, beta-carotene, oral charcoal, 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.

In summary, we described the typical clinical and biochemical findings of CEP in a young Taiwanese male. In the past, most patients have died by the age of 40 years, however, improvements in supportive care (particularly the use of antibiotics) have improved the prognosis, although the hematological complications may be fatal. Gene therapy by virus-mediated transfer of functional UROS cDNA into pathogenic hematopoietic stem cells has been reported in a mouse model, with complete and long-term enzymatic, metabolic, and phenotypic correction. This may be an important curative methodology in the future.

References