

# Erythropoietic Protoporphyria in a Family

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**Erythropoietic protoporphyria (EPP) is an autosomal dominant condition due to decreased activity of ferrochelatase. The disease is characterized by a wide range of photocutaneous changes and occasionally by liver disease. The level of protoporphyrin is raised in erythrocytes and it may also be increased in the feces. We report herein a case of EPP present in a family which was diagnosed by a high free erythrocyte protoporphyrin (FEP) count.**

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Erythropoietic protoporphyria (EPP) is an inherited metabolic disorder of porphyrin and is associated with the diminished activity of enzyme ferrochelatase (or heme synthetase)<sup>1</sup>, which is the last enzyme of the heme synthetic pathway, eventually resulting in the elevation of red blood cells, plasma, bile, and fecal protoporphyrin levels. Generally the disease manifests in childhood, clinically characterized by episodes of acute photosensitivity. The most common symptoms are painful burning and pruritus of the skin even to a minute solar exposure. Other symptoms may include erythema, edema, petechiae (less often), and solar urticaria. Skin lesions between acute attacks may be subtle and may consist of occasional crusting and excoriations of the exposed areas. Subsequently, a number of similar reactions will recur and, as a consequence, chronic skin changes will develop characterized by shallow scars and waxy thickening of the skin over the proximal finger joints, circumoral linear scars, atrophy of the rims of the ears, and persistent violaceous erythemas<sup>2,3</sup>.

There was no previously reported case of EPP

in Korea. The authors present a case of EPP present in a family diagnosed by an increased free erythrocyte protoporphyrin (FEP) count.

## REPORT OF A CASE

A 24-year-old man visited our clinic due to a burning sensation of the skin following solar exposure and subsequent excoriations and crust formations at the exposed areas since the age of 7. Family history revealed similar symptoms in his mother, younger brother and some relatives. At the age of 16, during routine examination, his urinary uroporphyrin and coproporphyrin levels were checked which were all negative or within normal limits. On physical examination, numerous shallow linear punctate scars were seen on the whole face, mainly on the nose and cheeks (Fig. 1). The skin covering the knuckles was thickened and lichenified. MED for UVB was 40 mJ/cm<sup>2</sup> and a provocation test was performed on the back and arm with 100J/cm<sup>2</sup>, 200J/cm<sup>2</sup> of UVA and 100mJ/cm<sup>2</sup>, 200mJ/cm<sup>2</sup> of UVB. After 24 hours, UVA left pigmentation and UVB left erythema. However, artificial solar radiation with a solar simulator showed painful swelling at the exposed site after 20 minutes of exposure. Biopsy specimens obtained from erythema induced by phototest and the face showed amorphous, hyaline-like materials around the superficial blood vessel walls which was positive in PAS stain (Fig.

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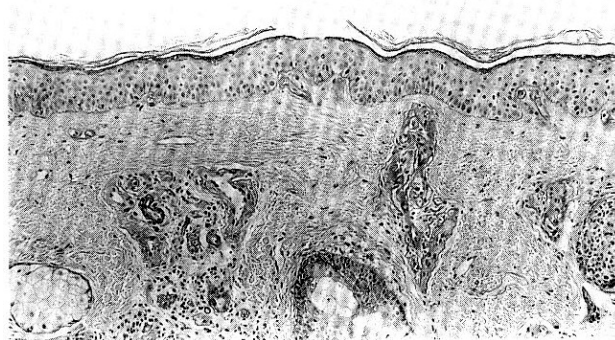
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**Fig. 1.** Numerous shallow lineal punctate scars were on the whole face, mainly on the nose and cheeks.

2). No deposition of IgG and C<sub>3</sub> were seen at the basement membrane zone and perivascular areas by direct immunofluorescence technique. The following laboratory data were normal; hemoglobin concentration, white blood cell counts, platelet count, erythrocyte sedimentation rate, serum urea nitrogen and electrolyte concentrations, liver function test and antinuclear antibody titer. A porphyrin screening test for urine and urinary uroporphyrin and coproporphyrin was negative. In screening tests for blood and stools, red fluorescence of the porphyrin was seen in wood light. FEP level was elevated to 1,381  $\mu\text{g/dl}$  RBC (normal, 13.1 to 55.1  $\mu\text{g/dl}$  RBC for male, 20.2 to 59.4  $\mu\text{g/dl}$  RBC for female)<sup>4</sup> by modifying Piomelli *et al.*'s method of acid extraction technique<sup>5,6</sup>. This was performed as follows: first, we added 200  $\mu\text{l}$  of 5% celite suspension to a conical centrifuge tube of 12 ml capacity, and added 100  $\mu\text{l}$  of well-mixed EDTA anticoagulated whole blood and mixed it



**Fig. 2.** Amorphous, hyaline-like materials around the superficial dermal blood vessel walls which was positive in PAS stain (H & E stain  $\times 100$ ).

by vortexing for 10 seconds. Then we added 4 ml of ethyl acetate: acetic acid solution to solubilize porphyrin and vortexed it for 10 seconds. We centrifuged the solution for 5 minutes with 1,000 g and poured the supernatant into another tube completely. There we added 4ml of 1.5 mol/L HCl and vortexed it for 30 seconds and centrifuged again for 5 minutes at the same speed. The lower HCl layers were aspirated with the serum separators and measured with a luminescence spectrometer (fluorometer), Perkin Elmer®, model LS-5. The excitation wavelength was 405 nm, the emission wavelength was 600 nm and the slit wavelength was 10 nm. We repeated measurements of the absorbances of each sample twice against a blank of 1.5 mol/L HCl. The calculation was as follows.

$$\mu\text{g protoporphyrin/dL RBC} = \frac{\text{fluor (unkn)} \times \text{conc (std)} \times 4.6 \times 100 \times 100}{\text{fluor (std)} \times 0.1 \times 1.11 \times \text{Hct (\%)}}$$

fluor (unkn) = fluorescence absorbance of unknown sample

fluor (std) = fluorescence absorbance of standard

conc (std) = concentration of standard, 1  $\mu\text{g/ml}$

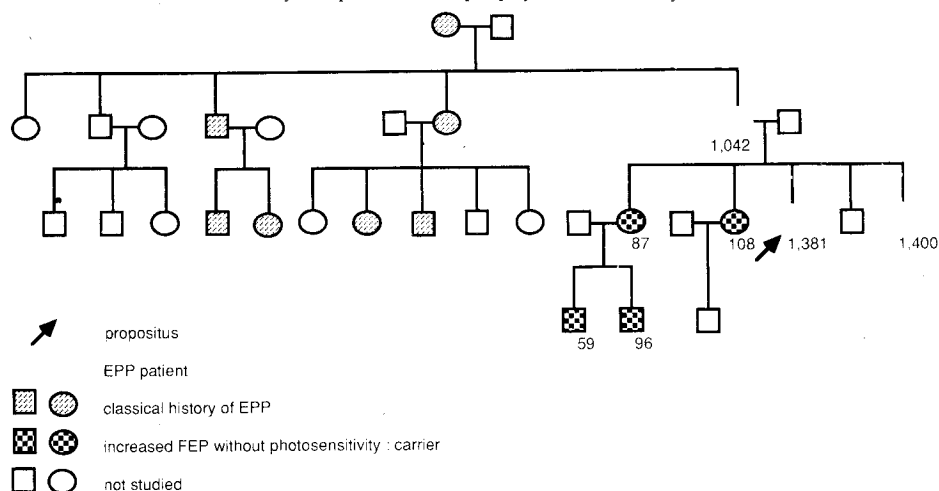
4.6 = final volume (ml) of porphyrins in HCl

0.1 = volume of blood used for assay

1.11 = correction for use of a coproporphyrin fluorescence standard to measure protoporphyrin fluorescence

100 = conversion factor of hematocrit from % to a decimal fraction

100 = conversion factor from "per ml" to "per dl"



**Fig. 3.** Representative pedigrees of a family affected by erythropoietic protoporphyria. The numbers next to the figures indicate the protoporphyrin content of erythrocytes, measured in micrograms per dl RBC. EPP; erythropoietic protoporphyria, FEP; free erythrocyte protoporphyrin.

The FEP levels of the patient's family were measured in two symptomatic members (mother and brother) and four asymptomatic members (2 sisters and 2 nephews) (Fig. 3). His mother and brother had markedly elevated FEP levels: 1,042 and 1,400  $\mu\text{g}/\text{dl}$  RBC and the others showed only slight elevation; 87, 108, 59 and 96  $\mu\text{g}/\text{dl}$  RBC in two sisters and two nephews. Because the beta-carotene tablet was not available in the Korean market, we recommended application of sunscreens with a high sun protection factor. Therapy with sunscreens did not lead to any definite improvement of photosensitivity.

## DISCUSSION

Although EPP is a rare condition, it is one of the two most common porphyrias, along with porphyria cutanea tarda<sup>3</sup>. The biochemical product formed in excess in EPP is protoporphyrin. Since it is insoluble in water, this chemical is found in red blood cells and excreted in feces but not in urine. Because of the lack of increased porphyrins or porphyria precursors in the urine, this was one of the last porphyrias to be clearly defined<sup>7,8</sup>. The problem is compounded when the diagnosis is suspected clinically and then dismissed after an initial negative screening test. A common complaint is an intense burning pain occurring within 10-30 minutes of exposure to sun-

light, and persisting for several hours. It is possible that this subjective feature may be the only clinical evidence of disease and may not be followed by an objective sign such as redness, swelling or scarring, so that children with EPP may be regarded as neurotic, nervous or hysterical<sup>9</sup>. A small number of patients develop fatal liver disease and there is some evidence that early intervention can improve the outcome<sup>10</sup>, and oral iron therapy has been known to exacerbate some cases of EPP<sup>11</sup>. For the above reasons, it is important not to miss the diagnosis. Using the solvent extraction qualitative screening test, among 11 cases of EPP, 7 were missed by the initial screening test<sup>12</sup>. Recently fluorescence microscopy of erythrocyte was recommended as the screening test of choice in the detection of increased red cell porphyrins because it is more sensitive and simpler in method than the traditional qualitative test<sup>13</sup>. Demonstration of elevated levels of free protoporphyrin in erythrocyte, plasma and often in stools confirms the diagnosis<sup>3</sup>. In our case, the patient was not diagnosed as EPP at first in spite of the typical clinical symptoms. Later we were able to arrive at a diagnosis of EPP by measuring the FEP level.

The first familial study of EPP was reported in 1963 by Haeger-Aronsen and Krook<sup>8</sup> and, in general, EPP was considered to be transmitted by simple dominant heredity. Thereafter, so many

**Table 1.** Porphyrin studies of the family members of the patient

| Subjects       | Age       | Sex      | Symptom of EPP | Porphyrin screen tests |       |       | FEP ( $\mu\text{g/dl}$ RBC) |
|----------------|-----------|----------|----------------|------------------------|-------|-------|-----------------------------|
|                |           |          |                | Urine                  | Stool | Blood |                             |
| Mother         | 60        | F        | +              | —                      | ND    | +     | 1,042                       |
| Sitster        | 37        | F        | —              | —                      | ND    | —     | 87                          |
| Sitster        | 33        | F        | —              | —                      | ND    | —     | 108                         |
| <b>Patient</b> | <b>24</b> | <b>M</b> | <b>+</b>       | —                      | +     | +     | <b>1,381</b>                |
| Brother        | 17        | M        | +              | —                      | +     | +     | 1,400                       |
| Nephew         | 14        | M        | —              | —                      | ND    | —     | 59                          |
| Nephew         | 12        | M        | —              | —                      | ND    | —     | 96                          |

EPP: erythropoietic protoporphyria

FEP: free erythrocyte protoporphyrin (normal range M: 13.1-55.1, F: 20.2-59.4)

ND: not done

patients with EPP have been reported that the disorder was found to be transmitted as an autosomal dominant trait, with many carriers and few clinically involved individuals<sup>14,15</sup>. These studies indicate that the disease is transmitted in an autosomal dominant manner with variable penetrance<sup>2,14,15</sup>. However, alternative hypothesis involving more complex mechanisms of inheritance are offered, such as an autosomal recessive condition in a three-allele system<sup>16,17</sup>. If this hypothesis is correct, one would not usually expect parent-to-child transmission of the disease. Our patient had nine clinically affected relatives showing transmission of the trait from parent to child (Fig. 3). Although we were not able to perform extensive family studies, clinical family history suggested autosomal dominant transmission of the disorder. Four asymptomatic members of the family had elevated FEP levels without iron deficiency anemia and lead poisoning (Table 1). They were asymptomatic carriers with increases FEP levels.

Although EPP is generally considered to be a relatively benign disease of cutaneous photosensitivity usually unassociated with systemic manifestations, a number of cases associated with abnormalities of the liver, biliary tract and hematopoiesis have been reported<sup>2,8,14,18</sup>. In addition to simple avoidance of the sun or use of a high sun protection factor sunscreen, ingestion of beta-carotene often ameliorates the photosensitivity of patients to the point that some can lead essentially normal lives<sup>2,19</sup>. Cholestyramine has been shown to reduce photosensitivity and to

decrease hepatic protoporphyrin content<sup>20</sup>. Liver disease become manifest in 5-10% of the patients<sup>21</sup>. Usually mild but occasionally fatal liver cirrhosis is recorded with extremely high erythrocyte protoporphyrin levels and abnormal liver function test results<sup>20</sup>. Thus it may be prudent to advise all patients with EPP to keep in close touch with their physicians and to have their blood protoporphyrin levels and liver function tests monitored at least yearly and whenever symptoms of photosensitivity change in intensity.

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