

## ERYTHROPOIETIC PROTOPORPHYRIA

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**Abstract.** This is the first report of erythropoietic protoporphyria in Norway. In two families, 6 patients with manifest and 9 subjects with latent disease were found. The pedigrees suggested an autosomal dominant inheritance with variable expression. Porphyrin screening tests on blood and faeces are recommended in all cases of photosensitivity. By these tests all the manifest cases of erythropoietic protoporphyria can be detected. However, these tests are usually not sufficiently sensitive to disclose all latent cases, in which time-consuming quantitative analyses may also fail. In these cases fluorescence microscopy of red blood cells is a reliable and rapid diagnostic procedure.

Erythropoietic protoporphyria (EP) has been diagnosed with increasing frequency since first defined and described by Magnus et al. in 1961 (9).

Biochemically, EP is fundamentally different from the cutaneous hepatic porphyrias and congenital erythropoietic porphyria (Günther's disease) so far as there is no increase of porphyrins or their precursors in the urine. The belated recognition of EP is probably due to this fact, because the diagnosis porphyria usually is discarded in the absence of porphyrinuria. The biochemical characteristics of EP are greatly increased amounts of protoporphyrin, and to a lesser extent, of coproporphyrin in the erythrocytes and usually also in the faeces. Red fluorescing erythrocytes (fluorocytes) are found in the peripheral blood and the bone marrow.

In the cutaneous hepatic porphyrias erythrocyte porphyrins are normal. Hitherto, EP was regarded as a purely cutaneous form of porphyria. Donaldson (4), however, recently reported a fatal case due to development of hepatic cirrhosis with bleeding oesophageal varices. He called attention to the possibility of severe liver disorder complicating EP. EP is characterized by the onset of

photosensitivity in early childhood. Light sensitivity is less severe than in Günther's disease, and persists throughout the patient's lifetime, sometimes with decrease of sensitivity. Intense burning and itching of the skin followed by erythema develop within a few minutes of exposure to sunlight. The reaction is restricted to the exposed parts of the skin and usually subsides within 12-24 hours. The nose, cheeks, ears, lips and the backs of the hands are particularly afflicted. Secondary changes in the form of superficial crusted ulcers leaving depressed scars, and coarse thickening of the skin are frequently seen. Thickening and furrowing of the lips and circumoral linear scars further appear to be typical signs. Vesicular and bullous lesions are usually not seen, although hydroa aestivale-like eruptions have been reported (13). A few reports describing other clinical manifestations such as eczematization (10, 12), lipid proteinosis (2, 8) and Quinckes oedema (1) have appeared.

Histological and histochemical examinations of the skin changes have shown hyaline deposits particularly around the vessels in the papillae and the upper corium (7, 8, 11).

The wavelengths responsible for provoking the photosensitivity are in the region of 400 nm, corresponding to the maximal action spectra of porphyrins (9). Window glass therefore gives no protection.

EP seems to be inherited as a dominant character (6, 15).

### MATERIAL AND METHODS

The material consists of 33 subjects from 2 unrelated families A and B, out of which 3 and 2 subjects respectively are our original patients, who have suffered from

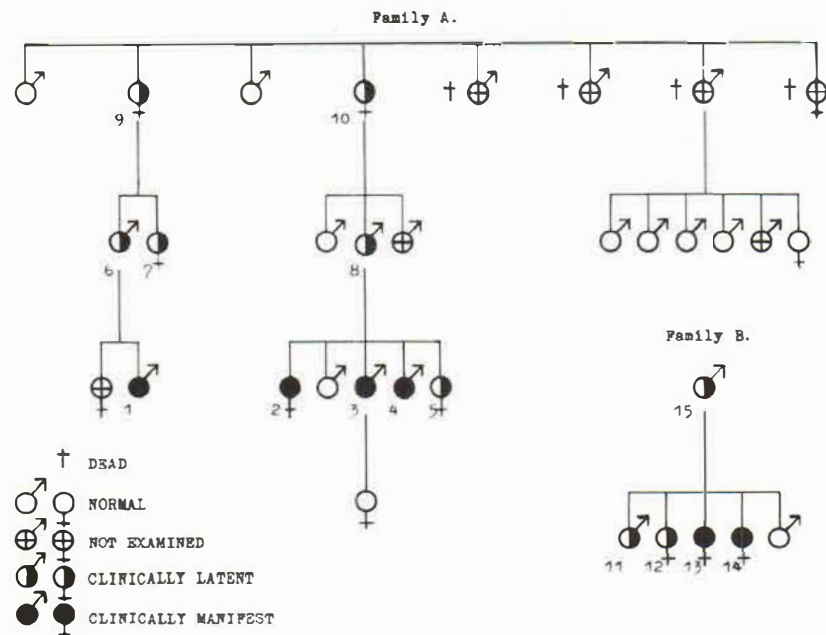


Fig. 1. Pedigrees of two families with erythropoietic protoporphyria.

light sensitivity since early childhood. There is no consanguinity between any of the parents, and none of the parents or siblings of these 5 patients have ever been similarly afflicted.

### CASE REPORTS

The 3 patients of family A are a woman aged 21 and her two brothers aged 20 and 27 years. The patients of family B are sisters aged 22 and 24 years. The history, clinical picture and course of the disease are essentially similar in all the 5 patients and can be summarized as follows:

From the age of 1 to 2 years a few minutes of exposure to sunlight has caused intense burning, erythema and swelling of the skin of the face, neck and dorsa of the hands and other parts unduly exposed. Intense or prolonged exposure has resulted in development of crusted ulcers leaving depressed scars. Blister formation has never been observed. The symptoms have appeared early in the spring, have persisted during the summer and subsided during the autumn and winter. However, symptoms may have occurred on bright days even during the winter. Window glass has given no protection. The abnormal reaction to sunlight has almost completely prevented normal outdoor activities during childhood and adolescence. Considerable improvement has been noted during later years, a fact which they all consider as mainly due to better understanding of the necessity of protection against sunlight.

The 3 patients of family A were admitted to the Department of Dermatology in 1955 and 1956, and the 2 patients of family B in 1961. Essentially similar cutaneous manifestations were found in all the 5 patients: Erythematous swelling and thickening of the skin of the face and dorsa of the hands, scattered crusted ulcers on the

bridge of the nose and crusted rhagades on the lips. Physical examination and laboratory results including examination of urine for porphyrins revealed nothing abnormal. The condition was interpreted as a light dermatosis, suggestive of hydroa aestivale, although vesiculo-bullous lesions were not observed. Treatment with antimalarials and sun-screening creams gave no satisfactory results. The 3 patients of family A were re-examined in September 1970 and presented identical cutaneous manifestations: Waxy complexion of the nose and cheeks with atrophic depressed scars, linear scars around the mouth and thickened lips with marked furrowing. The skin of the backs of the hands was thickened and lichenified. The skin changes made all the patients look older than their years. Physical examination and routine laboratory tests, including ESR, blood counts, liver function tests, haemoglobin, serum iron and TIBC, were normal. Porphyrin screening tests on blood and faeces were positive, while porphyrin screening test on urine was negative. Further chemical analyses revealed greatly increased amounts of protoporphyrin, and to a lesser extent, of coproporphyrin in blood and faeces. A high percentage of fluorocytes were found in peripheral blood.

The 2 patients of family B had moved to a distant area and could not be re-examined clinically. However, blood samples were obtained and examined for porphyrins with essentially similar results as those of the patients of family A. For practical reasons samples of faeces and urine were not obtained. Based on these findings the diagnosis EP was made in all these 5 patients.

Subsequently 28 members of the 2 families were examined as follows: Porphyrin screening test in blood and fluorescence microscopy of erythrocytes were performed as described by Cripps & Peters (3). For quantita-

tive determination of porphyrins in erythrocytes and faeces the extraction method described by Rimington et al. (14) was used. Two ml were used for analysis. The extracted proto- and coproporphyrins were scanned in a Beckman DB-G spectrophotometer. Base-line absorption at maximum between 398-403 nm and 406-411 nm was determined graphically. The values were not corrected for losses of proto- and coproporphyrin during analysis.

## RESULTS

Fig. 1 shows the pedigrees of families A and B. Two normal parents of the original 5 patients and 5 normal descendants of family A are excluded from the pedigrees. Patients 2, 3, 4, 13 and 14 are the propositi. It will be seen that the investigation revealed 1 additional subject with manifest EP, totalling 6 persons with manifest disease. A further 9 latent carriers of EP were found. All the manifest and latent cases in family A are found in two ascending lines in accordance with autosomal dominant inheritance.

In Table I are presented the results of quantitative determinations of erythrocyte protoporphyrin, blood porphyrin screening tests and fluorescence microscopy in the 15 manifest and latent cases. In patient no. 12 fluorocytes were not found at the first examination. Since increased amounts of protoporphyrin were found in her erythrocytes, a re-examination was made, and a few fluorocytes could be detected. In all the other cases a varying number of fluorocytes were observed at the first examination.

For practical reasons, stool samples for quantitative analysis were obtained from only 8 subjects, namely the 4 patients with manifest disease, the father of the propositi and 3 normal members of family A. The amounts of protoporphyrin varied from slightly to greatly increased (112-1 300  $\mu\text{g/g}$  dry weight) in the patients with manifest disease, and 2 of these also had increased amounts of coproporphyrin (23-24  $\mu\text{g/g}$  dry weight). In the remaining subjects the results were within normal values.

## COMMENTS

This is the first report of erythropoietic protoporphyria in Norway. The late recognition of these cases as cases of porphyria is due to the fact that porphyrin analysis previously has been limited to the urine in cases of light sensitivity. EP probably

Table I. Clinical symptoms related to the content of erythrocyte protoporphyrin, presence of fluorocytes, and screening test for blood porphyrins in 15 subjects with manifest and latent erythropoietic protoporphyria

| Pat. no. | Symptoms | Erythrocyte protoporphyrin $\mu\text{g}/100$ ml | Fluorocytes | Screening test blood |
|----------|----------|---|-------------|----------------------|
| Family A |          |   |             |                      |
| 1        | Moderate | 1 085   | +++         | ++                   |
| 2        | Severe   | 2 440   | +++         | +++                  |
| 3        | Severe   | 3 350   | +++         | +++                  |
| 4        | Severe   | 4 070   | +++         | +++                  |
| 5        | None     | 37  | +           | Negative             |
| 6        | Probably | 46  | +           | Negative             |
| 7        | None     | 35  | +           | Negative             |
| 8        | None     | 80  | ++          | Negative             |
| 9        | Probably | 254   | ++          | +                    |
| 10       | None     | 131   | +           | +                    |
| Family B |          |   |             |                      |
| 11       | None     | 117   | +           | Negative             |
| 12       | None     | 95  | (+)         | Negative             |
| 13       | Severe   | 1 315   | +++         | +++                  |
| 14       | Severe   | 1 120   | +++         | +++                  |
| 15       | None     | 25  | +           | Negative             |

occurs more frequently than previously assumed. A complete investigation of photosensitivity therefore should include porphyrin examination of blood and faeces.

The rapid and simple screening tests described by Cripps & Peters (3) have greatly facilitated the laboratory diagnosis of EP. By these screening tests all manifest cases can be detected. These tests are, however, not sufficiently sensitive to disclose all the clinically latent cases, which are usually found in larger numbers than manifest cases in families with EP.

In the present study the screening test on blood was weakly positive in 2 and negative in 7 latent carriers of the disease. In these 9 subjects the diagnosis was established by the finding of fluorocytes. Quantitative porphyrin analyses are time-consuming and require the services of a laboratory experienced in porphyrin analysis. Furthermore, too much weight should not be placed on a single quantitative determination.

Some disagreement exists concerning the upper normal limit of erythrocyte protoporphyrin, varying from 20 to 65  $\mu\text{g}/100$  ml red cells (6, 10). Some authors regard 50-52  $\mu\text{g}/100$  ml red cells as the upper normal limit (3, 5, 16, 18). Regarding 50  $\mu\text{g}/100$  ml red cells as the upper normal limit,

4 of the latent cases in our study had normal amounts of protoporphyrin in the blood. This is in accordance with the fact that in EP as well as in other types of porphyria the latency may be chemical as well as clinical.

In the cases of latency, fluorescence microscopy proved to be the only useful diagnostic method. Surmond et al. (17) asserted that in latent cases the number of fluorocytes may be very small and therefore missed at routine examination. Since fluorocytes seem to be predominantly young cells, they recommended separation of these cells by centrifugation. As will be recalled (Table I), fluorocytes were not found in our subject no. 12 at the first examination, and in this case the method recommended might have been useful. In our experience, however, this procedure is usually unnecessary. Of the chemically latent subjects, nos. 6 and 15 have given birth to offspring with manifest disease, a fact which gives the genetic proof of the reliability of fluorescence microscopy in these cases. Further evidence in this respect is the fact that fluorocytes were never found in 5 offspring of healthy family members and in 8 normal controls.

Our 6 patients with manifest disease all seem to have experienced some decrease in light sensitivity with increasing age, although they still are severely disabled. Two of the subjects with latent disease (nos. 6 and 9) probably had symptoms of light sensitivity during childhood. Our study seems to confirm previous suggestions of an autosomal dominant inheritance of this disease.

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Received February 25, 1971

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