

## CLINICAL REPORT

**Familial and Sporadic Porphyria Cutanea Tarda: Clinical, Biochemical and Genetic Features with Emphasis on Iron Status**ANETTE BYGUM<sup>1</sup>, LENE CHRISTIANSEN<sup>2</sup>, NIELS ERIK PETERSEN<sup>2</sup>, MOGENS HØRDER<sup>2</sup>, KRISTIAN THOMSEN<sup>3</sup> and FLEMMING BRANDRUP<sup>1</sup>*Departments of <sup>1</sup>Dermatology and <sup>2</sup>Clinical Biochemistry and Clinical Genetics, Odense University Hospital, Odense, Denmark and the <sup>3</sup>Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark*

The manifestation of porphyria cutanea tarda reflects genetic and environmental factors. Mutations in the uroporphyrinogen decarboxylase gene, located at chromosome 1p34, discriminate familial porphyria cutanea tarda from sporadic cases. Furthermore, mutations in the haemochromatosis gene may be involved in the aetiology. In this study 53 unrelated Danish patients with porphyria cutanea tarda were classified according to uroporphyrinogen decarboxylase and haemochromatosis gene mutations and the genotype related to the clinical and biochemical data. Thirteen patients (25%) had familial porphyria cutanea tarda. The results signify the advantage of DNA diagnostics for identification of familial cases, as anamnestic data are doubtful and erythrocyte uroporphyrinogen decarboxylase activity measurements insufficient for correct classification. Eight patients with porphyria cutanea tarda (15%) were homozygous for the haemochromatosis gene C282Y mutation and 8 patients were heterozygous. Patients homozygous for the haemochromatosis related mutation showed biochemical evidence of excessive iron storage as well as increased urine porphyrin excretion levels. This seems to confirm a relationship between porphyria cutanea tarda and haemochromatosis. No differences were found between patients with sporadic and familial porphyria cutanea tarda regarding age of onset, clinical severity, sex distribution, liver function tests and iron storage parameters. However, daily alcohol intake and use of oestrogens were reported more frequently in the group of sporadic patients. It was found that women were over-represented in our study. **Key words:** genetics; haemochromatosis; phenotype; porphyria cutanea tarda; uroporphyrinogen decarboxylase gene mutations.

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Porphyria cutanea tarda (PCT), named by Waldenström in 1937 (1), is characterized clinically by cutaneous lesions on light-exposed areas. The photosensitization is caused by accumulated porphyrins in the skin deriving from

decreased activity of uroporphyrinogen decarboxylase (UROD), the fifth enzyme in the haem biosynthetic pathway. The cutaneous symptoms include skin fragility with blister formation, erosions, hypertrichosis, pigmentation and premature ageing of the skin. The clinical diagnosis is verified biochemically by elevated urinary concentrations of uroporphyrins, heptacarboxylic porphyrin, and other acetic-acid substituted porphyrins. Increased concentrations of heptacarboxylic porphyrin and isocoporphyrin are found in the faeces (2, 3).

Manifestation of active disease depends on extrinsic factors including alcohol, oestrogens, polyhalogenated aromatic hydrocarbons (PAH), hepatotropic viruses and iron. At least 80% of patients with PCT have some degree of hepatic haemosiderosis, ranging from mild to severe iron overload (4, 5) and about 40% of British or Danish patient populations with PCT carry the haemochromatosis related *HFE* mutation, C282Y, in either heterozygous or homozygous form (6, 7). Hepatitis C and HIV infections are now also firmly implicated in the precipitation of PCT (8–10). Occasionally, PCT may be a skin marker of hepatocellular carcinoma (11).

PCT is traditionally divided into two groups based on measurement of erythrocyte UROD activity and family history (2, 12). 10–20% of cases belong to the familial PCT (fPCT), which is inherited as an autosomal dominant trait associated with mutations in the gene encoding UROD. In fPCT the UROD activity is decreased in all cells (2, 12). fPCT is characterized by an incomplete penetrance, as 90% of the gene mutation carriers remain asymptomatic life long (2); 80–90% of cases belong to the group of sporadic PCT (sPCT) in which the decreased UROD activity is restricted to the liver (13) and there is no family history of the disorder. The liver-specific enzyme defect does not appear to be caused by mutation at the UROD locus. Hepatoerythropoietic porphyria (HEP) is the rare homozygous form of fPCT, characterized by a 75–90% reduction in UROD activity in all cells (2).

The gene encoding UROD has been mapped to chromosome 1p34 (14). The genetic basis of PCT is heterogeneous, as more than 40 different mutations in the UROD gene have been characterized so far (15) (see also Human Gene Mutation Database: [www.uwcm.ac.uk/uwcm/mg/hgmd0.html](http://www.uwcm.ac.uk/uwcm/mg/hgmd0.html)). The broad spectrum of

mutations might possibly influence the phenotypic expression of PCT. This aspect, however, has not yet been addressed in detail.

In this study the relationship between the genotype (the mutations in the UROD gene) and the phenotype (the clinical and biochemical data) was examined in 53 unrelated Danish patients. Furthermore, our aim was to identify the environmental risk factors of importance for the clinical expression in predisposed patients.

## MATERIAL AND METHODS

The study was based on a protocol, informed consent and approval by the Local Ethics Committee.

### Patients

The study included 53 unrelated Danish patients (24 males and 29 females), previously diagnosed as PCT by an experienced dermatologist according to distinctive objective clinical findings, typical abnormal urine porphyrin profile with elevated urinary uroporphyrins, heptacarboxylic porphyrin, and other acetic-acid substituted porphyrins, and no history of neurovisceral attacks. Furthermore, a positive response to treatment supported the diagnosis of PCT as opposed to other cutaneous porphyrias. Thirteen patients were consecutively referred and the data for 40 were retrieved from the medical record files covering the period 1987 to 1999. At the time of inclusion, PCT was clinically overt in 36 patients and in remission in 17.

### Data collection

Clinical features, exogenous precipitating factors, course of disease and familial occurrence of PCT were recorded. Laboratory investigations included excretion patterns of porphyrins, iron metabolic parameters, liver transaminases, serological testing for hepatitis B, C and HIV as well as ultrasonography of the liver, and liver biopsy when indicated. In the newly referred cases (1997–1999), standardized, baseline clinical and biochemical examinations were performed and for patients selected from medical record files relevant clinical and biochemical data were retrieved retrospectively from case records, and were thus incomplete for 40 patients. When biochemical data had been measured repeatedly, the initial values were chosen, as some biochemical features are influenced by treatment with phlebotomy and hydroxychloroquine.

A scoring system ranging from 0 to 10 was established in order to rank the clinical variations in the individual patients, enabling comparisons between single individuals and groups of patients. Each of the 10 different clinical features (see Table I) scored 1 point when present. Cumulated clinical scores for individual patients are presented in Table II.

### Mutation detection and UROD activity assay

The genetic discrimination between fPCT and sPCT patients was based on mutation screening of the UROD gene, as previously described (15). Erythrocyte UROD enzyme activity was determined in 38 of the patients, essentially as described elsewhere (16).

### Statistics

Statistical analyses and data summaries were performed using the STATA 6.0 software (Stata Corporation). When testing

differences between groups, the Wilcoxon rank sum test was used for ordinal data and Fisher's exact test was used for categorical data.

## RESULTS

A positive family history of PCT among first-degree relatives was obtained in 6 (11%) of the 53 patients included in the study. Seven different, putative disease-related mutations were identified in DNA from 13 (25%) patients. Two of these mutations were found in 3 and 5 individuals, respectively (15). We did not observe any cases of hepatoerythropoietic porphyria. Measurements of the erythrocyte UROD activity in 38 patients demonstrated a tendency to a bimodal distribution (see Fig. 1), with the fPCT patients exhibiting values between 3.7 and 6.8 nkat/l (median: 4.1 nkat/l) and the values measured in the sPCT patients ranging from 6.4 to 23.5 (median: 10 nkat/l). There were no apparent differences in the residual erythrocyte UROD activity between individuals with the different UROD mutations (results not shown).

Detailed clinical data of skin manifestations were available for only 45 patients. The frequency of the different skin manifestations is reported in Table I. In Table II the number of evaluated patients is given and the clinical and biochemical features for the 53 patients with PCT are summarized in relation to the results of the UROD mutation analysis.

No correlation was found between a high urinary porphyrin excretion and a high clinical score (results not shown). Grouping according to gender revealed a borderline significant difference in age at onset (males: mean age = 53, females: mean age = 46,  $p = 0.052$ ) and a significant difference in alcohol as a potential precipitating factor (males: 100%,  $n = 14$ , females: 67%,  $n = 18$ ,  $p = 0.024$ ).

Sixteen patients carried at least one copy of the C282Y

Table I. Clinical findings in 45 patients with porphyria cutanea tarda

Clinical findings	Patients <i>n</i> (%)
1. Blisters/erosions on hands	42 (93)
2. Blisters/erosions on face	28 (62)
3. Fragile skin	21 (47)
4. Self-reported photosensitivity	3 (7)
5. Hypertrichosis	25 (56)
6. Hyperpigmentation	15 (33)
7. Miliae	16 (36)
8. Scleroid changes	2 (4)
9. Dark urine	12 (27)
10. Other (e.g. scarring, premature ageing of the skin, photo-onycholysis or scarring alopecia)	21 (47)

Each clinical feature (1–10) scored 1 point when present. Cumulated clinical scores for individual patients are shown in Table II.

Table II. Clinical and biochemical features and exposure to precipitating factors for patients with sporadic porphyria cutanea tarda (sPCT) and familial porphyria cutanea tarda (fPCT)

	sPCT (total number 40)	fPCT (total number 13)
	Median (range)	Median (range)
Age of onset ( $n=33/13$ ) <sup>1</sup>	50 (34–74)	51 (26–67)
Clinical score (0–10) ( $n=36/13$ )	4 (2–6)	4 (2–6)
Total urine porphyrins $\mu\text{M}^2$ ( $n=31/9$ )	3.7 (0.36–29)	7.9 (3.6–18.3)
Total fract. urine porphyrins $\mu\text{M}^{3,4}$ ( $n=9/4$ )	3.9 (0.1–33.8)	4.1 (3.7–11.1)
	Positive results $n$ (%)	Positive results $n$ (%)
“Known liver disease” <sup>5</sup> ( $n=23/10$ )	22 (96)	8 (80)
Abnormal liver biopsy <sup>6</sup> ( $n=13/4$ )	11 (85)	4 (100)
Abnormal liver ultrasonography ( $n=20/13$ )	13 (65)	5 (38)
Abnormal s-ferritin ( $n=31/13$ )	24 (87)	10 (77)
Abnormal liver transaminases ( $n=34/13$ )	23 (68)	7 (54)
S-transferrin-iron saturation $\uparrow^7$ ( $n=26/11$ )	7 (27)	3 (27)
Relapse of disease <sup>8</sup> ( $n=40/13$ )	8 (20)	4 (31)
Daily alcohol consumption ( $n=23/9$ )	21 (91)	5 (56)
Oestrogen treatment in women <sup>9</sup> ( $n=14/5$ )	9 (64)	1 (20)
Iron supplements ( $n=13/4$ )	5 (38)	3 (75)
Hepatitis C ( $n=19/11$ )	0 (0)	1 (9)
Hepatitis B ( $n=40/13$ )	0 (0)	0 (0)
Polyhalogenated aromatic hydrocarbons ( $n=40/13$ )	0 (0)	0 (0)
HIV ( $n=5/9$ )	1 (20)	0 (0)

<sup>1</sup>Number for which data are available for sPCT and fPCT, respectively.

<sup>2</sup>Reference interval  $<0.6 \mu\text{M}$ .

<sup>3</sup>Reference interval  $<0.6 \mu\text{M}$ .

<sup>4</sup>Total fractionated porphyrin values are given in cases where total porphyrin values are not available.

<sup>5</sup>Covers overall information on liver disease, such as increased levels of liver enzymes, abnormalities discovered by ultrasonography, liver biopsies or from the patients themselves.

<sup>6</sup>Steatosis, haemosiderosis or fibrosis.

<sup>7</sup>Transferrin iron saturation is regarded as increased when above 50% for women and 60% for men.

<sup>8</sup>Clinical and biochemical rebound.

<sup>9</sup>Synthetic oestrogens for oral contraception or postmenopausal symptoms.

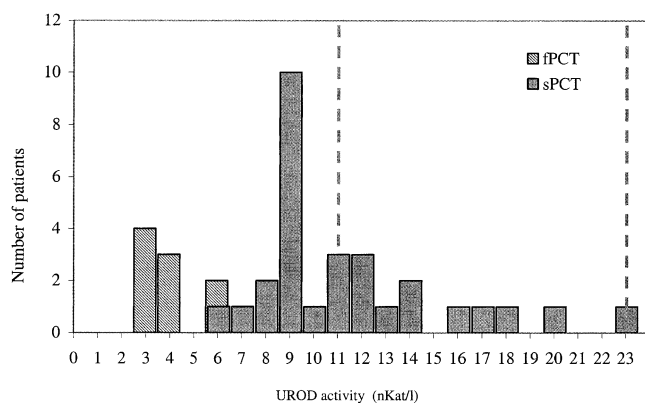


Fig. 1. Measurements of the erythrocyte uroporphyrinogen decarboxylase (UROD) activity in 38 patients in relation to the initial separation into familial porphyria cutanea tarda (fPCT) and sporadic porphyria cutanea tarda (sPCT) based on mutational analyses. Dotted lines indicate lower and upper reference limits for healthy donors.

mutation and 8 (6 with sPCT and 2 with fPCT) were homozygotes. Comparisons of clinical and biochemical features of PCT patients grouped according to homozygosity for C282Y are summarized in Table III.

## DISCUSSION

The most common skin manifestations in our patients were blisters and erosions on the dorsal aspect of hands and fingers. This reflects the most frequent reason for examination of the urine porphyrin excretion. Hypertrichosis and fragile skin were seen in about half the patients and hyperpigmentation in about one third. Registration of fragile skin was based on anamnestic information given in the medical records. This finding seems to be underestimated, as blisters, erosions or ulcers may reflect vulnerable skin. Very few patients noticed the harmful effect of sun exposure, probably owing to the retarded skin reaction in relation to sun exposure. In order to grade the clinical symptoms, a scoring system was worked out ranking the clinical expression in the individual patients (see Table I). The purpose of our scoring system is to give an idea of the clinical expression and is not a severity score per se. Based on the medical records, the score could be assessed in 45 patients. All patients, for which the data were available, had a clinical score of at least 2, i.e. they presented with at least two of the most prevalent clinical symptoms listed in Table I; no

Table III. Clinical and biochemical features for non-homozygous C282Y and homozygous C282Y patients with porphyria cutanea tarda

	HFE 282C/C and 282C/Y (n=45)	HFE 282Y/Y (n=8)
	Median (range)	Median (range)
Age of onset (n=38/8) <sup>1</sup>	50 (26–74)	48 (39–67)
Clinical score (0–10) (n=37/8) <sup>1</sup>	4 (2–6)	3 (2–6)
Total urine porphyrins $\mu\text{M}$ (n=35/5) <sup>1,2</sup>	4.1 (0.36–29)	10.2 (3.7–13.7)
Total fractionated urine porphyrins $\mu\text{M}$ (n=9/2) <sup>1,3</sup>	4 (0.1–33.81)	3.3 (2.95–3.72)
S-ferritin $\mu\text{g L}^{-1}$ (n=39/5) <sup>1,4</sup>	513 (22–3686)	890 (675–1191)
S-aspartate aminotransferase $\text{U L}^{-1}$ (n=16/1) <sup>1,5</sup>	59.5 (18–160)	34 (34–34)
S-alanine aminotransferase $\text{U L}^{-1}$ (n=27/6) <sup>1,6</sup>	61 (18–180)	43.5 (35–214)
S-alkaline phosphatase $\text{U L}^{-1}$ (n=38/7) <sup>1,7</sup>	215.5 (106–671)	199 (119–252)
	No. of positive results (%)	No. of positive results (%)
“Known liver disease” <sup>8</sup> (n=27/6) <sup>1</sup>	24 (89)	6 (100)
Abnormal liver biopsy <sup>9</sup> (n=11/5) <sup>1</sup>	9 (82)	5 (100)
Abnormal liver ultrasound (n=28/5) <sup>1</sup>	14 (50)	4 (80)
S-transferrin-iron saturation $\uparrow$ <sup>10</sup> (n=31/6) <sup>1</sup>	5 (16)	5 (83)
Relapse of disease <sup>11</sup> (n=45/8) <sup>1</sup>	12 (27)	0 (0)
Daily alcohol consumption (n=28/5) <sup>1</sup>	23 (82)	3 (60)
Oestrogen treatment in women <sup>12</sup> (n=17/1) <sup>1</sup>	8 (47)	1 (100)
Iron supplements (n=15/2) <sup>1</sup>	8 (53)	0 (0)

<sup>1</sup>Number for which data are available for HFE 282C/C and 282C/Y, and HFE 282Y/Y, respectively.

<sup>2</sup>Reference interval  $<0.6 \mu\text{M}$ .

<sup>3</sup>Reference interval  $<0.6 \mu\text{M}$ .

<sup>4</sup>Reference interval 15–300  $\mu\text{g L}^{-1}$ .

<sup>5</sup>Reference interval 10–50  $\text{U L}^{-1}$ .

<sup>6</sup>Reference interval 10–50  $\text{U L}^{-1}$ .

<sup>7</sup>Reference interval 70–250  $\text{U L}^{-1}$ . The reference intervals given are those used at the Department of Clinical Biochemistry and Clinical Genetics, Odense University Hospital. Combined intervals for men and women are given.

<sup>8</sup>The term “known liver disease” covers overall information on liver disease, such as increased levels of liver enzymes, abnormalities discovered by ultrasound scanning, liver biopsies or from the patients themselves.

<sup>9</sup>Steatosis, haemosiderosis or fibrosis.

<sup>10</sup>Transferrin iron saturation is regarded as increased when above 50% for women and 60% for men.

<sup>11</sup>Clinical and biochemical rebound.

<sup>12</sup>Synthetic oestrogens for oral contraception or postmenopausal symptoms.

difference was noticed between the scores of patients with sPCT or fPCT.

In recent years molecular genetics has provided a more convenient method for easy and reliable diagnosis of the porphyrias. Based on mutational analysis, 13 (25%) of our patients have fPCT (15). Interestingly, only 6 of these were recognized as familial cases based on family history, thus demonstrating the low penetrance of fPCT. However, some fPCT cases might have been due to new gene mutations.

Determination of the erythrocyte UROD activity in 38 of the patients allowed for a comparison of the power to discriminate fPCT from sPCT using DNA diagnostics and enzymatic analysis, respectively. The indication of a bimodal distribution of UROD enzyme activity observed correlated fairly well with the mutational-based grouping of the patients into familial and sporadic cases (Fig. 1). However, some of the enzyme activities measured in patients assumed to be sporadic fell below the normal range and one of the samples actually overlapped with the activity determined in the group of familial cases. This is

in keeping with previous findings that some of the normal erythrocyte UROD activity measurements fall into a “grey area” in the low normal range or even below this, making discrimination based on erythrocyte activity alone difficult (17, 18). This result thus signifies the beneficial use of DNA diagnostics for identification of familial cases as well as latent or asymptomatic carriers in affected families.

Comparison of the clinical and biochemical features of fPCT patients carrying the different UROD gene mutations did not reveal any difference in any of the parameters studied. However, as the mutations associated with fPCT are often found in only one or a few families, the resulting low sample sizes limit the appropriate conditions for such studies.

The results demonstrate that the median of total urine porphyrin excretion was significantly higher in fPCT patients compared to sPCT patients (7.9  $\mu\text{M}$  versus 3.7  $\mu\text{M}$ ,  $p=0.015$ ), and when only total fractionated urine porphyrin measures were accessible, a similar difference was seen, although this was not statistically

significant. These results may suggest that the UROD deficiency is more severe in the familial subtype of PCT in accordance with the assumed lower endogenous UROD activity caused by the UROD gene mutations. However, although the porphyrin excretion may be more pronounced in fPCT, this is not reflected in the clinical or in the additional biochemical parameters. Thus, there was no difference in the age at onset, clinical score, liver function tests and iron storage tests between the two groups of sPCT and fPCT patients. These findings are to some degree in disagreement with previous assumptions. Thus, it is generally believed that fPCT cases develop manifest disease at an earlier age than sPCT cases, although not many publications actually report on specific findings regarding this issue (19, 20). Partly confirming the results of this study, however, Siersema et al. (19) found that there was no difference in biochemical features between the two groups, except that the amount of porphyrin crystals in the liver was significantly higher in fPCT patients than in sPCT patients.

In patients examined for liver disease transaminases were elevated in 64%, ultrasonography of the liver was abnormal in 55% and 88% had abnormal liver biopsy with steatosis, haemosiderosis or fibrosis. This is in agreement with other studies reporting abnormal liver function tests in a high proportion of patients (21) and with the general assumption that almost all patients with PCT have some degree of liver abnormality. Liver disease in PCT is usually asymptomatic but a frequency of hepatocellular carcinoma of 5 to 16% of patients with PCT has been reported. The highest rate was seen in autopsy materials (11, 22, 23). We did not see any case of hepatocellular carcinoma, probably because of the relatively young age of our patients.

Seventy-nine percent of the patients had increased iron storage (raised s-ferritin and/or s-transferrin-iron saturation above 50% for women and 60% for men). A relationship between hepatic haemosiderosis, which is present in most patients with PCT, and hereditary haemochromatosis has been confirmed (4, 6, 24). Among the identified haemochromatosis-related mutations in the *HFE* gene (25, 26), the C282Y mutation appears to be the most prominent regarding iron overload and this mutation may have an influence on the development and clinical signs of PCT. Eight (15%) of the patients included in the present study were homozygous for C282Y, three of whom met the current clinical diagnostic criteria for haemochromatosis (27). The remaining 5 patients were not specifically examined for or diagnosed as having haemochromatosis.

The proportion of patients with increased transferrin-iron saturation was significantly higher in C282Y homozygotes than in non-homozygotes (83% versus 16%,  $p=0.003$ ), as expected. Furthermore, a considerable, but non-significant difference in both s-ferritin levels (median 890  $\mu\text{g/l}$ ,  $n=5$  versus median 513  $\mu\text{g/l}$ ,  $n=39$ ,  $p=0.073$ )

and total urine porphyrin excretion (median 10.2  $\mu\text{M}$ ,  $n=5$  versus median 4.1  $\mu\text{M}$ ,  $n=35$ ,  $p=0.14$ ) was found, with C282Y homozygotes exhibiting the highest values. This indicates that the increased iron storage, mediated by the C282Y mutation, has an aggravating effect on the biochemical parameters and may lead to a more severe course of PCT. However, the number of homozygotes in this study is too small for any conclusions to be drawn. A recently published study (28) showed that homozygosity for the C282Y mutation was associated with an earlier onset of skin lesions in both familial and sporadic PCT, and screening for the *HFE* mutation in all patients with PCT may be a tool to identify patients at risk of severe complications.

A total of 35 patients were interviewed regarding exogenous, provoking factors. In 33 (94%) of these at least one, provoking factor could be identified (daily alcohol intake, oestrogen treatment, iron supplements, hepatitis). Ethanol ingestion was the single most frequent factor, as 81% reported a daily alcohol intake. Furthermore, the results showed a significantly higher proportion of sPCT patients admitting to regular alcohol consumption than fPCT patients (91% versus 56%,  $p=0.038$ ), and a substantial, but non-significant difference in the number of oestrogen users between the sPCT group and the fPCT group (64% versus 20% of females,  $p=0.14$ ). The finding of an increased proportion of sPCT patients exposed to alcohol and oestrogens could suggest that the requirement of additional precipitating factors is more decisive for development of the sporadic subtype of PCT. This is not surprising, as the presence of an UROD mutation must be regarded as a major, single risk factor in itself. There was only one HCV-positive patient and no HBV-positive patients, consistent with previous findings of a lower frequency of hepatitis as a precipitating factor in Northern European populations (9) compared to the population living around the Mediterranean Sea.

Women were slightly over-represented in our material (29 females versus 23 males). Previously, PCT was held to be more prevalent in males (3, 29) but there seems to be a changing patient profile probably owing to the widespread ingestion of oestrogenic hormones and an increased consumption of alcohol by women in recent decades. In accordance with this, we found that 53% of the women included in the study had received oestrogen treatment and 67% had a daily alcohol intake. A selection bias in favour of women cannot be totally excluded, owing to the fact that women are more likely to consult a doctor.

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