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CLINICAL REPORT

Porphyria Cutanea Tarda in a Swedish Population: Risk Factors and Complications

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There are varying reports on the prevalence of risk factors in porphyria cutanea tarda (PCT). We reviewed 84 patients with PCT in a restricted uptake area in Gothenburg, Sweden and evaluated different potential risk factors for the disease and complications. Besides a thorough medical history, the patients were investigated with urinary porphyrin analyses, transferrin saturation, ferritin and liver tests. Subsamples of patients were tested for antibodies to hepatitis C virus (n=68), haemochromatosis gene mutations (n=58) and with the oral glucose tolerance test (n=31). We found a prevalence of about 1 patient with PCT in 10 000 inhabitants. Nineteen (23%) patients reported heredity for PCT. Identified risk factors were alcohol abuse (38% of male patients), oestrogen treatment (55% of female patients), anti-hepatitis C virus positivity (29% of male patients), diabetes (17%) or impaired glucose tolerance (45% of tested patients) and haemochromatosis gene mutations (57% of tested patients). All patients positive for anti-hepatitis C virus belonged to the non-hereditary group. During follow-up we observed a high incidence of stroke, no case of hepatocellular carcinoma and a normal life expectancy.
Key words: porphyria cutanea tarda; hepatitis; haemochromatosis; diabetes mellitus; life expectancy.

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Porphyria cutanea tarda (PCT), the most common type of porphyria, is associated with a reduced activity of the enzyme uroporphyrinogen decarboxylase (UROD) (1), which catalyses the fifth step in the biosynthesis of haem. Accumulation of porphyrins in the liver causes liver damage and their circulation in plasma gives rise to a phototoxic skin reaction. The disease exists in a sporadic (S-PCT=type I) and a familial autosomal dominantly inherited form (F-PCT=type II). In S-PCT decreased UROD activity is restricted to the liver, whereas in F-PCT UROD activity is reduced in all tissues. To date more than 50 different UROD mutations have been identified (Human Gene Mutation database: www.uwcm.ac.uk/uwcm/mg/hgmd0.html) (2).

Additional genetic or non-genetic factors are needed for overt disease. Known provoking factors are iron, alcohol, oestrogen and hepatotropic virus infection such as hepatitis C virus (HCV), all of which are associated with inhibition of hepatic UROD activity (3–5). Reports from different countries vary widely regarding the importance of different factors for the induction of the disease. For example, reports from southern Europe (6, 7), Japan (8) and the USA (5, 9) indicate a very great importance of HCV for the phenotypic expression of PCT, with figures varying between 56% and 85%. This is in contrast to northern France (10), Germany (11), Czechoslovakia (12) and New Zealand (13), where PCT is less often associated with HCV (positivity rates varying between 0 and 23%).

There are also differences in the reported incidence of hepatocellular carcinoma in PCT, varying between 1.4% in Denmark and Sweden (14), 13% in the Netherlands (15), 30% in Japan (8) and 34% in Italy (16). Such differences may, at least in part, be due to inherent differences in the prevalence of hepatitis B and C in the different populations.

The aim of the present investigation was to study the prevalence of potentially inducing factors for PCT and the incidence of complicating factors, e.g. malignant disease, in a low endemic area for HCV.

MATERIALS AND METHODS

This is a retrospective study of 84 patients with PCT. The uptake area concerning PCT includes the city of Gothenburg in the south-western part of Sweden (475 000 inhabitants) and its surroundings. Since 1978 almost all patients living in Gothenburg and many patients from the surrounding area with a new diagnosis of clinically overt PCT have been referred to the Department of Dermatology at the Sahlgrenska University Hospital and have been treated and followed up by one of the authors (I.R.R.). Based on a check-up at the Central Laboratory for Clinical Chemistry, which serves the whole Gothenburg area, there were no analyses diagnosing PCT for patients living in Gothenburg which had not been referred to the Department of Dermatology. Thus, the patients included in the present study comprise virtually all patients with the disease in the city of Gothenburg and many from the surrounding area during the years 1978–2001. The demographics of the patients are given in Table I. By the end of 2001, 21 patients were deceased, 3 had moved, 6 were lost to follow-up and 54

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Table I. *Demographics and risk factors for porphyria cutanea tarda (PCT) at the time of diagnosis*

Parameter*	*n*	%	Women	Men
Patients	84		31	53
Age at onset, mean ± SD (range)	55 ± 13 (9–81)		59 ± 12 (29–81)	52 ± 14 (9–76)
Heredity for PCT	19/84	23	9/31	10/53
CYS/CYS	8/58	14	4/24	4/34
CYS/HIS	6/58	10	4/24	2/34
Anti-HCV positivity	13/68	19	1/27	12/41
Alcohol abuse	21/84	25	1/31	20/53
Oestrogen	17/31	55	17/31	0
Diabetes mellitus	14/84	17	5/31	9/53
Impaired glucose tolerance	14/31	45	7/12	7/19
Barbiturates	3/84	3.6	2/31	1/53
Cytostatics	3/84	3.6	0	3/53
Blood transfusion	2/84	2.3	1/31	1/53
No identified risk factor	11/84	13	1/31	10/53

*A patient may have more than one risk factor.
CYS, C282Y; HIS, H63D.

(31 men and 23 women) were still under observation. The mean follow-up time for the total study was 8.7 years (range 1–23).

The diagnosis was based on the characteristic clinical features, i.e. skin fragility, blistering on sun-exposed areas on the hands and face and sometimes milia, facial hypertrichosis and hyperpigmentation, together with the typical urinary porphyrin pattern of marked increases in uro- and heptacarboxy-porphyrins. Faecal porphyrins were analysed in 70 of the 84 patients. Porphyrins in urine were concentrated by absorption to calcium phosphate before elution with HCl and determination by spectrophotometry. Porphyrins were concentrated and converted to their methyl ester derivatives before separation by thin-layer chromatography. Faecal porphyrins were extracted with ether from an acidified sample. Coproporphyrin was extracted from the ether with HCl 0.1 mol/l, protoporphyrin with HCl 1 mol/l. The concentration was determined by spectrophotometry. One patient was found to have porphyria variegata. The oral glucose tolerance test was done in 31 patients who did not have clinically overt diabetes mellitus. Sixty-eight patients were tested for antibodies to HCV by enzyme-linked immunosorbent assay and recombinant immunoblot assay. HCV RNA was analysed by PCR assay. A test for hepatitis B was done in 78 patients, with no positive results. In 80 patients a test for antinuclear factor (ANA) was done because of reported co-existence of systemic lupus erythematosus (SLE) and PCT (17), findings not confirmed in later studies (18, 19).

The diagnosis of familial PCT (F-PCT) was based on the information that one first-degree relative had an established diagnosis of PCT. The lack of enzyme or mutational analysis is explained by the fact that these methods were not available during a large part of the study period. Alcohol abuse was diagnosed when the patient admitted to daily or almost daily consumption. Analysis for mutations of the haemochromatosis gene (HFE), C282Y (CYS) and H63D (HIS), was performed in 58 patients who were available when this testing was introduced during the later part of the study period.

Comparisons of continuous variables were made using ANOVA. Comparisons of nominal data and frequencies were made using the contingency table: p values < 0.05 were regarded as significant.

The ethical committee of the hospital approved this follow-up study.

RESULTS

As stated previously, besides many patients from the surroundings of Gothenburg, probably all patients with PCT in the uptake area of Gothenburg are included in the present study. Based on the Gothenburg patients, i.e. 45 patients living in the city of Gothenburg by the end of 2001, the prevalence of PCT in this area is about 1 in 10 000 inhabitants.

Nineteen (23%) patients reported heredity for PCT. About every third male patient admitted to alcohol abuse, but only one woman. Half the female patients were on oestrogen treatment, postmenopausal in all except two patients. Almost every third tested male patient but only one woman out of 27 was positive for anti-HCV. All patients positive for anti-HCV belonged to the non-hereditary group. Every sixth patient had diabetes and in addition, almost half the tested patients had impaired glucose tolerance (Table I).

There was no significant relationship between having diabetes mellitus or a positive glucose tolerance test and having homozygous CYS/CYS or compound heterozygous CYS/HIS state.

As is evident from Table II, 33 of 58 (57%) tested patients were positive for HFE gene mutations. Eight patients were CYS homozygous, six patients were compound heterozygous and one was HIS homozygous. The positivity rate was somewhat higher in the hereditary group. However, this difference was not statistically significant. Seven of eight CYS homozygous patients had a haemochromatosis phenotype, defined as having a transferrin saturation of $>45\%$ as well as a serum ferritin value above the upper limit of normal (20). As a matter of fact, all these patients had a transferrin saturation of $>65\%$. In the CYS/HIS compound heterozygous group, only one of six patients fulfilled these criteria. Blood transfusion seemed to be a precipitating factor for PCT in one CYS homozygous

Table II. *Haemochromatosis (HFE) genotype in relation to iron phenotype (mean ± SD) in 58 patients with porphyria cutanea tarda*

Genotype	*n*	%	Transferrin saturation (%)	Serum-ferritin × ULN
C282Y/C282Y	8	14	74 ± 16	2.75 ± 0.76
C282Y/H63D	6	10	53 ± 14*	1.09 ± 0.23
H63D/H63D	1	1.7	29	1.293
C282Y/WT	7	12	46 ± 11*	1.93 ± 0.24
H63D/WT	11	19	39 ± 11*†	1.66 ± 0.55
WT/WT	25	43	39 ± 11*†	1.89 ± 0.61

ULN, upper limit of normal. Ferritin ULN for women = 140 μg/l; ferritin ULN for men = 230 μg/l.
*Significantly lower than in C282Y homozygous ($p < 0.05$).
†Significantly lower than in compound heterozygous ($p < 0.05$).

patient and in one patient who was not tested for HFE gene mutations but who had phenotypic features of haemochromatosis.

The iron phenotype for the HFE-analysed patients is shown in Table II. There were no significant differences in serum ferritin between the groups, but CYS homozygous patients had higher serum iron and transferrin saturation indices than the other groups.

Three patients had positive titres for antinuclear factor. Two of these proved to have a contemporary SLE according to American Rheumatism Association (ARA) criteria.

During the follow-up period, 15 patients (12 men and 3 women) experienced stroke. Their mean age at the time of the stroke was 70 years (range 50–80).

Twenty-one patients died after a median follow-up time of 10 years (range 1–20). Their mean age at diagnosis was 66 years. Their mean age at death (which in 18 of 21 patients occurred during the years 1991–2000) was 86 years for women and 76 years for men, i.e. not lower than in the general population, which in the Gothenburg area was 81 and 74 years, respectively, during this period. As liver cancer is reported as a frequent cause of death in patients with PCT, data from the Causes of Death Register were obtained from the National Institute of Statistics. In 17 of the patients the cause of death was established without autopsy. Six patients had cancer: two had cancer of the lungs, one malignant brain tumour, one renal cancer, one colon cancer and one cancer of the stomach with metastases. Three autopsied patients had coronary infarction, the remaining patients died from various causes.

Ten of the 21 deceased patients had had stroke, in two cases fatal.

DISCUSSION

The prevalence of PCT in our area is substantially lower than has been reported from Spain (21) but notably higher than in the USA (3). The difference from the prevalence in Spain may at least to some extent be explained by differences in the prevalence of risk factors for expression of the disease, e.g. HCV load.

The frequency of hereditary PCT, as based on a family history of PCT, was 23% in the present study. Admittedly, history of PCT is not 100% specific or sensitive for the true prevalence of PCT. However, the prevalence of F-PCT in the present investigation is close to the frequency of F-PCT in other studies, in which enzyme or mutational analyses have been performed (22, 23).

The prevalence of anti-HCV positivity in PCT reported in the literature varies widely; according to a recent review it is between 4 and 92% (24). In the present study, none of the patients with a family history of PCT was anti-HCV-positive, whereas 13 of 52 (25%) patients with 'spontaneous' PCT had this risk factor. In those publications in which it is stated whether the anti-HCV-positive patients belonged to the hereditary group of patients or not, contradictory results have been reported concerning the prevalence of anti-HCV positivity in the patients with hereditary PCT (5, 6, 9). As to the patients with spontaneous PCT, there is no doubt that the prevalence in our patient population is very high in comparison with the prevalence of anti-HCV positivity in the general Swedish population, which is about 0.37% (25). Notably, this prevalence is low compared with many other countries, e.g. Italy, where the anti-HCV prevalence is 3.2% (26). Thus, the higher rate of anti-HCV positivity in patients with PCT from southern Europe may to some extent be related to the difference in 'basal' anti-HCV prevalence.

We observed no difference in the prevalence of HFE gene mutations between hereditary and spontaneous PCT, irrespective of whether all forms of mutations were taken into consideration, or only the CYS homozygous plus compound heterozygous. The prevalence of HFE gene mutations observed in the present material (58%) is lower than that reported in some studies (5) but higher than reported in other studies (27). Differences in the basal prevalence of HFE gene mutations between different populations are well known (28–30), and may be one contributory factor for the differences in reported prevalence of HFE gene mutations in patients with PCT (5, 31–33).

As to other risk factors, the figures on alcohol abuse in the present study are presumably unreliable, as the information was not based on any accepted method for reliably revealing high alcohol consumption. The high prevalence of diabetes mellitus and high rate of abnormal glucose tolerance test is consistent with earlier observations (34, 35).

Judged from the present study, the survival time is not by any means influenced by the disease. This is clearly related to the low prevalence of HCV in our patients, as well as to the fact that we observed no case of hepatocellular carcinoma in this study. Linet et al. (14) in an epidemiological study from Denmark and Sweden, based on 530 patients, observed a significantly increased risk of hepatocellular carcinoma in PCT. The incidence observed in that study was about 1%. Our data are not in contrast to this observation. As our total study population comprised only 84 patients, it is conceivable that we did not observe any case of hepatocellular carcinoma in our series. However, much higher incidence rates for hepatocellular carcinoma have been reported from Holland (15) and Italy (16). The first report was based on a low number of patients and may have been associated with a selection bias. In the Italian report, 90% of the patients also had HCV infection, and 88% of the cancer patients already had cirrhosis, a well-known risk factor for hepatocellular carcinoma in liver disease. Thus in our opinion, the question as to whether PCT predisposes to hepatocellular carcinoma remains unsettled. The mortality in all forms of cancer in the present study (28%) does not differ substantially from the cancer-related mortality in Sweden.

A new observation is the high rate of stroke in the present study. Harmsen et al. (36) in a population study of inhabitants in Gothenburg found that 2.3% of 70-year-old subjects had a positive history of stroke. This should be compared with our figure of 17.9% of patients having had stroke at a mean age of 70 years. The mean age of all our 84 patients at follow-up was 63 years. We have no explanation for this high stroke incidence. It has been suggested that iron accumulation results in an increased risk for stroke, but recent studies (37) did not provide evidence supporting this hypothesis in patients with HFE gene mutations. Notably, the stroke events in the present study did not occur in the patients with diagnosed haemochromatosis. However, all patients died before the HFE gene analysis was available, which is why we cannot exclude the possibility that the stroke patients had this disease. Thus, our observation needs confirmatory studies.

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