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Porphyria cutanea tarda in Scotland: underlying associations and treatment approaches

Chayada Chaiyabutr,[1,2] Robert Dawe,[2,3] Sally H. Ibbotson,[2] Tara Clarke,[2] and Victoria A. McGuire,[2,3]

[1]Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, [2]Scottish Photobiology Service, Photobiology Unit, University of Dundee & NHS Tayside, Ninewells Hospital & Medical School, Dundee, UK; and [3]Scottish Cutaneous Porphyria Service, Photobiology Unit, University of Dundee & NHS Tayside, Ninewells Hospital & Medical School, Dundee, UK

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Correspondence
Robert Dawe
Scottish Photobiology Service, Photobiology Unit
University of Dundee & NHS Tayside
Ninewells Hospital & Medical School
Dundee DD1 9SY
UK
E-mail: robert.dawe@nhs.scot

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Abstract

Background Despite its rarity, porphyria cutanea tarda (PCT) is globally recognized as the most common form of cutaneous porphyria. This study aims to review the underlying associations and treatment of PCT in Scotland.

Methods We retrospectively reviewed data on 27 patients diagnosed with PCT between 1987 and 2022 at the Scottish Cutaneous Porphyria Service.

Results Males slightly predominated (66.7%). The mean ± standard deviation (SD) age at diagnosis was 55.6 ± 12.5 years. Common associated factors were heavy alcohol intake (88.5%), genetic hemochromatosis (72%), smoking (45.5%), and hepatitis C virus infection (16%). Most had multiple associated factors (70.4%). Patients with genetic hemochromatosis with the C282Y genotype exhibited higher median transferrin saturation (69.5 vs. 35, $P = 0.004$) and ferritin levels (observed in males only) (1175 vs. 339; $P = 0.014$) than those with the H636D genotype. Most (52%) received combination therapy of venesection and antimalarials, followed by venesection monotherapy (32%) and antimalarial monotherapy (16%). Overall, 95.2% achieved biochemical improvement. Median time to improvement was 7, 5, and 9 months with venesection, antimalarial, and combined treatments, respectively ($P = 0.173$). Biochemical remission was achieved in 50% of patients. Remission occurred in 2/4 of patients with antimalarial monotherapy (median time 19 months) and 9/13 patients with combined treatment (median time 26 months). Biochemical relapse was found in three patients, all of whom received combination therapy.

Conclusion Excess alcohol intake and genetic hemochromatosis were the most common underlying associations with PCT in our Scottish cohort. Treatment for PCT should be individualized, and long-term follow-up is needed to monitor for disease relapse.

Introduction

Porphyria cutanea tarda (PCT) is the most common form of cutaneous porphyria worldwide. The prevalence in Dundee, Scotland, was estimated to be 1 in 13,000 population.[1] PCT can affect both sexes but is slightly more common in males.[2] It usually commences in the 5th–6th decades of life.[2] It arises as a consequence of decreased activity of uroporphyrinogen decarboxylase (UROD) in the liver, resulting in an accumulation of uroporphyrinogen and other intermediates.[2] The phototoxic nature of these porphyrins, which are elevated in blood and skin, particularly at the dermo-epidermal junction, leads to blistering and fragility of photo-exposed skin.[3]

PCT can be divided into three types: type 1 (sporadic or acquired—UROD is produced normally but is inactivated) accounting for 80% of cases; type 2 (inherited or familial—having heterozygous mutations in UROD, resulting in 50% reduction in this enzyme activity) accounting for almost 20% of cases; and type 3 (a very rare inherited familial type without mutations in UROD but with liver UROD activity affected and normal UROD in the blood).[2] To have overt clinical manifestations of PCT, the activity of UROD has to decrease to lower than 20% of normal activity.[2,4] PCT requires precipitating/triggering factors to cause disease, even in inherited PCT, and most patients with PCT will have more than one triggering factor.[5] The most commonly observed PCT-associated

precipitating factors include excess alcohol intake, hepatitis C virus (HCV) infection, hereditary hemochromatosis, human immunodeficiency virus (HIV) infection, and, probably, estrogen intake.[2]

In addition to the mainstays of visible light photoprotection and avoidance of skin trauma, the main disease-targeted therapeutic approaches for PCT comprise phlebotomy and low-dose 4-aminoquinoline drugs (particularly chloroquine and hydroxychloroquine). These two treatments have different modes of action, contraindications, convenience, and costs, and a combination of these treatments is also used. As PCT is an uncommon disease and there were not many studies reporting on therapeutic efficacy,[3,4,6–8] our objectives were to (1) assess the associated precipitating causes and (2) the treatment responses of PCT in patients in Scotland.

Material and methods

Study approval was obtained from the NHS Tayside Caldicott Guardian Committee (IGTCAL11263). We retrieved data from all patients diagnosed with PCT at the Scottish Cutaneous Porphyria Service from 1987 to 2022. Demographic data associated with precipitating factors, biochemical results, and treatment response data were collected. "Heavy alcohol drinking" was defined as patients recorded with a history of drinking more than 14 units/week or having a history of heavy drinking documented in their medical records.

Porphyrin biochemistry was performed to diagnose PCT, including plasma porphyrin scan,[9] total urine, and when a stool sample was provided, total fecal porphyrin quantification followed by urine/fecal porphyrin profiling by high-performance liquid chromatography (HPLC).[10,11] The thresholds for an abnormally high level of urine uroporphyrin over 24 h were >41 μg/24 h or an unusually high total urine porphyrin/creatinine (TUP/Cr) ratio over 27 nmol/mmol. Before 2002, our hospital used urine uroporphyrin over 24 hours to diagnose PCT, which was then replaced by the TUP/Cr ratio due to the ease of spot urine collection.

Biochemical improvement was determined when the level of urine uroporphyrin 24-h or TUP/Cr decreased twofold, while biochemical remission was determined when urine uroporphyrin 24-h or TUP/Cr decreased into the normal population range (95% reference interval). Biochemical relapse was defined as a result of patients' biochemical remission, followed by a subsequent increase in 24-hour urine uroporphyrin or TUP/Cr ratio above the normal population range. The duration of follow-up time was defined by the period between the first and last urine porphyrin laboratory tests.

Treatment data were categorized into three groups: venesection monotherapy, oral antimalarial monotherapy, and a combination of venesection and antimalarials. Venesection was first performed at 2–3-week intervals and then gradually reduced in frequency, as guided by ferritin levels. The frequency and volume (usually 300 mL) of phlebotomies differ among patients, depending on the extent of iron overload and any concomitant conditions. Once iron levels return to a normal range (usually aiming for low normal ferritin), patients transition to a maintenance phase of venesection, during which blood may be withdrawn two to four times a year, depending on the rate of iron reaccumulation. Antimalarial was prescribed only in low doses (oral chloroquine 200 mg base or hydroxychloroquine 200 mg once or twice weekly). Chloroquine is typically preferred over hydroxychloroquine in our PCT treatment due to our greater experience with its use in this condition. In addition, although all patients with PCT are advised to photoprotect and to use reflectant sunscreens perennially, compliance is an issue. Also, reliable data on photoprotection habits were difficult to ascertain from the records and, therefore, not available through this review.

The statistical analysis in this study used PASW Statistics for Windows (version 18; SPSS Inc., Chicago, IL, USA). Kaplan–Meier survival curves were used to determine the timing of biochemical improvement in PCT.

Results

A total of 27 patients were diagnosed with PCT during the 35-year study period. Men slightly predominated (18/27; 66.7%). The mean ± standard deviation (SD) age at diagnosis was 55.6 ± 12.5 years. The data relating to clinical features were retrieved and analyzed in 25 patients. The most common clinical presentations were blistering (23/25; 92%), skin fragility (19/25; 76%), and milia (13/25; 52%) on sun-exposed sites. Associated factors were heavy alcohol intake (23/26; 88.5%), genetic hemochromatosis (18/25; 72%), smoking (10/22; 45.5%), hepatitis C virus infection (HCV, 4/25; 16%), and human immunodeficiency virus infection (HIV, 1/8; 12.5%). There were no cases of hepatitis B virus infection or autoimmune hepatitis. Most patients had multiple associated factors (19/27,70.4%), mainly genetic hemochromatosis, heavy alcohol intake, and smoking. Our patients' most common hemochromatosis mutations were homozygous C282Y and homozygous H636D. Heterozygous C282Y, heterozygous H636D, and compound heterozygous C282Y/H636D were found in some patients (Table 1).

At first diagnosis, abnormally high ferritin levels were found in 73.3% (11/15) males and 87.5% (7/8) females. Median ferritin levels in men and women were 677 (range 238–1488) and 397.5 (range 90–829), respectively (normal range 30–400 μg/L for males; 13–150 μg/L for females). Abnormally high transferrin saturation was seen in 31.8% (7/22) of patients. Median transferrin saturation was 37% (range 16–93; normal range 22%–55%). Abnormally high alanine transaminase (ALT) was found in 60% (15/25). Median ALT was 65 (range 15–143; normal range 5–55) U/L. Most patients were diagnosed with PCT using a positive plasma scan, elevated TUP/Cr levels, and urine

Table 1 Demographic, clinical, and laboratory data of PCT patients categorized by receiving treatment

	Total (*n* = 27)		Venesection alone (*n* = 8)		Antimalarial alone (*n* = 4)		Combined treatment (*n* = 13)		
	n	%	*n*	%	*n*	%	*n*	%	*P*-value[a]
Demographics									
Sex: Male	18	66.7	6	75	2	50	8	61.5	0.741
Female	9	33.3	2	25	2	50	5	38.5	
Mean age at diagnosis (years, SD)	55.6	12.5	60.8	13.6	50.3	16.7	54.9	10.4	0.363
Median duration of symptom (months, IQR) (*n* = 22)	13.5	5.5, 72	15	3, 108	30	3.2, 66	12	6.72	0.966
Smoking (*n* = 22)									
Current	10	45.5	4	57.1	1	25	5	45.5	0.117
Ex-smoker	7	31.8	0	0	3	75	4	36.4	
Non	5	22.7	3	42.9	0	0	2	18.2	
Precipitating factor									
Heavy alcohol drinking (*n* = 26)	23	88.5	7	87.5	3	75	12	92.3	0.729
Hemochromatosis gene (*n* = 25)	18	72	5	71.4	4	100	9	69.2	0.673
Homozygous for C282Y	7	38.8	2	40	1	25	4	44.4	
Homozygous for H63D	4	22.2	2	40	1	25	1	11.1	
Heterozygous for H63D	3	16.7	0	0	1	25	2	22.2	
Heterozygous for C282Y	2	11.1	0	0	0	25	2	22.2	
Compound heterozygous for C282Y/H63D	2	11.1	1	20	1	25	0	0	
Current smoker (*n* = 22)	10	45.5	4	57.1	1	25	5	45.5	0.743
HCV infection (*n* = 25)	4	16	2	25	0	0	2	16.7	0.801
HIV infection (*n* = 8)	1	12.5	0	0	0	0	0	0	
Clinical (*n* = 25)			*N* = 8		*N* = 4		*N* = 12		
Blistering	23	92	6	75	4	100	12	100	0.123
Skin fragility	19	76	5	62.5	3	75	10	83.3	0.817
Milia	13	52	4	50	1	25	7	53.8	0.660
Scarring	10	40	6	75	2	50	2	16.7	0.047
Itching	8	32	3	37.5	2	50	3	25	0.616
Hypertrichosis	8	32	1	12.5	2	50	5	41.7	0.431
Hyperpigmentation	4	16	1	12.5	1	25	2	16.7	1.000
Sclerodermoid	0	0	0	0	0	0	0	0	—
Laboratory investigation at first diagnosis									
Median ferritin (μg/L, range)									
Male (*n* = 15)	677	238, 1488	643.5	246, 845	372.5	321, 424	997.5	238, 1488	0.259
Female (*n* = 8)	397.5	90, 829	336	253, 419	211	90, 332	520.5	376, 829	0.108
Median transferrin saturation (%, range) (*n* = 22)	37	16, 93	49	20, 73	34.5	16, 89	38	32, 93	0.805
Median ALT (U/L, range) (*n* = 25)	65	15, 143	71.5	25, 124	23.5	20, 38	73	31, 143	0.017
Median TUP/Cr (nmol/mmol, range) (*n* = 22)	448	78, 1461	470.5	182, 696	386	318, 1249	483	78, 1461	0.974
Treatment									
Median treatment duration of phlebotomy, (months), IQR	16	6, 52	5	4, 6.8	—	—	23	17.5, 129	<0.001
Median treatment duration of antimalarial drug (months), IQR	15	6, 23	—	—	21	1,24	14.5	6, 21.8	0.945
Median follow-up time (months), IQR	34.5	18.8, 129.3	19	8, 26	34.5	13.5, 48.8	119	23.5, 165	0.033

ALT, alanine aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; TUP/Cr, total urine porphyrin/creatinine ratio.

[a]*P*-value compared between venesection alone; antimalarial alone; and combined treatment group.

porphyrin profile to confirm the diagnosis (*n* = 22). Median TUP/Cr was 448 (range 78–1461) nmol/mmol (normal range <27 nmol/mmol).

In further analysis, we found that individuals with the homozygous or heterozygous C282Y genotype exhibited significantly higher median transferrin saturation (69.5 vs. 35, $P = 0.004$) and higher median ferritin levels (only observed in males; 1175 vs. 339; $P = 0.014$) compared to those with the homozygous or heterozygous H636D genotype (Table 2).

There were 25 patients for whom we could retrieve data relating to treatment outcomes. They were divided into three groups based on their management. The majority (13 patients; 52%) received the combination therapy of venesection and antimalarials. Venesection monotherapy was prescribed in eight patients (32%), and antimalarial monotherapy was used in four patients (16%). Baseline biochemical levels of ferritin, transferrin saturation, and TUP/Cr were not statistically different between these three groups, but baseline ALT levels were

Table 2 Laboratory investigation and treatment received based on the genotype of hemochromatosis.

	C282Y genotype (*n* = 9)		H636D genotype (*n* = 7)		
	n	**%**	***n***	**%**	***P*-value**[a]
Laboratory investigation at first diagnosis					
Median ferritin (μg/L, range)					
Male (*n* = 9)	1175	686, 1488	339	238, 424	0.014
Female (*n* = 5)	375	332, 419	425	253, 616	0.564
Median transferrin saturation (%, range; *n* = 15)	69.5	41, 93	35	22, 63	0.004
Median ALT (U/L, range; *n* = 15)	72.5	25, 143	61	20, 124	0.355
Median TUP/Cr (nmol/mmol, range; *n* = 14)	461	78, 1249	448	140, 1080	0.796

ALT, alanine aminotransferase; TUP/Cr, total urine porphyrin/creatinine ratio.
[a]*P*-value compared homozygous or heterozygous C282Y genotype and homozygous or heterozygous H636D genotype.

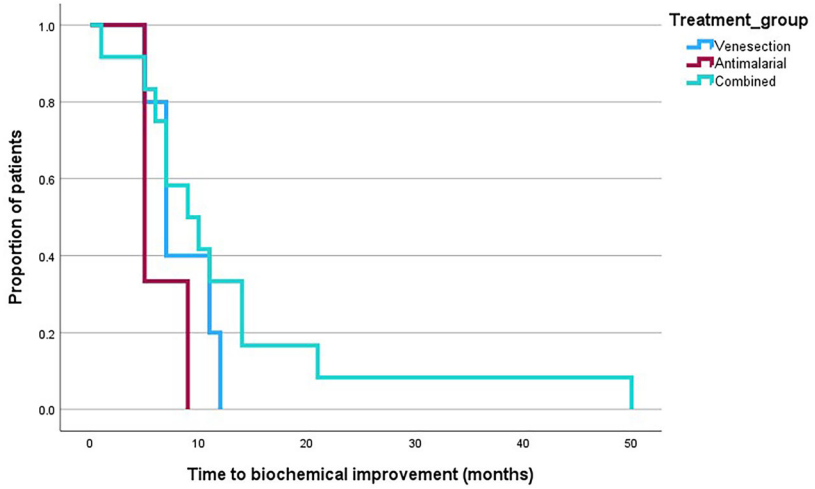

Figure 1 Time to biochemical improvement in PCT patients categorized by receiving treatment. The median time to improvement was 7, 5, and 9 months in venesection monotherapy, antimalarial monotherapy, and combined group.

significantly lower in those treated with antimalarials alone ($P = 0.017$).

When improvement was determined clinically, nearly all patients (24 of 25, 96%) reported a reduction in blistering and skin fragility after receiving treatment, except for one patient (in the antimalarial monotherapy group) who was drug-addicted and had poor compliance with treatment.

Biochemical change could be analyzed in 21 patients, and 20 out of 21 (95.2%) achieved biochemical improvement on treatment. The patient who did not achieve biochemical improvement was the aforementioned patient with poor compliance. The median time to improvement (range, determined in 20 patients) was 7 (5–12), 5 (5–9), and 9 (1–50) months with venesection, antimalarial, and combined treatments, respectively, which was not statistically different ($P = 0.173$; Figure 1). Data on biochemical remission could be analyzed in 22 patients and was achieved in 50% (11/22) of patients. Of the patients in remission, this was achieved in 2/4 (50%) who had received antimalarial monotherapy (median time to remission 19 months, range 8–30) and in 9/13 (69.2%) who had received combined venesection and antimalarials (median time 26 months, range 14–258). None of the patients who received venesection alone (0/5) demonstrated biochemical remission. Notably, the median time to biochemical remission was analyzed only in those who had achieved remission. Biochemical relapse was found in three patients, and all of these patients had received combined treatment with venesection and antimalarials. The median time to relapse was 22 months (range 17–178 months).

Minor side effects were reported in 6 patients (3 from venesection and 3 from antimalarials). Two patients developed anemia, and one felt faint with venesection. Nausea, diarrhea, and mild leukopenia were reported with antimalarials, and these adverse effects were reversible after drug cessation. No severe

side effects were reported, and notably, no adverse ophthalmological effects were reported in patients taking antimalarials.

Cancer diagnoses were also reviewed. One patient was diagnosed with prostate cancer before the diagnosis of PCT. Five patients were diagnosed with cancer after being diagnosed with PCT (two lung cancer, one hepatocellular carcinoma [when the PCT secondary to hemochromatosis had been well controlled for years], one colon cancer, and one lymphoma).

Discussion

This study revealed the associated and likely precipitating causes and treatment outcomes for patients with PCT in Scotland. The main underlying factors in our region were hemochromatosis and heavy alcohol intake. The prevalence of each precipitating factor in PCT varies depending on the study and location. For instance, mutations associated with hemochromatosis ranged from 21% to 73%, varying between studies.[2] The high prevalence of hemochromatosis in our PCT cohort may be linked to the high occurrence of C282Y and H63D mutations in the Celtic population. Previous studies have shown that 1% of newborns in Ireland were homozygous for C282Y and another 1% for homozygous H63D mutations.[12] In contrast, in the United States, where the population is quite racially diverse, the prevalence of homozygous C282Y and H63D genotypes was estimated to be 1.4 per 1000 and 12.7 per 1000 newborns, respectively.[13] Furthermore, in the United States, 70%–80% of PCT patients are identified as having concurrent HCV infection, contrasting with our current low occurrence of HCV in our cohort (16%).[2]

Iron overload plays a central pathogenic role in PCT, and ferritin and transferrin saturation measurements are usually used to assess the degree of excess iron. In our study, ferritin was a better marker of iron overload than transferrin saturation, as abnormally high ferritin levels were found in 73.3%–87.5% of patients, while high transferrin saturation was found in only 37%. However, one patient had high transferrin saturation with an average level of ferritin, indicating that the combination of ferritin levels and transferrin saturation is the most appropriate way to screen for iron status and overload in PCT.

Two specific treatments for PCT were used, which work through different mechanisms. Repeated venesection works by reducing iron overload and thus decreasing the formation of UROD inhibitors.[2] In contrast, 4-aminoquinolines (antimalarial drugs) work by increasing porphyrin excretion.[14] A previous study reported that venesection and antimalarials had comparable efficacy regarding time to remission.[7] Some centers prefer antimalarial treatment because of convenience, compliance, and cost.[4] However, venesection has been considered a first-line treatment for PCT in many centers, particularly for those with significant iron overload.[3] As antimalarial drugs do not affect iron status, PCT patients with hemochromatosis, or those with very high ferritin levels, as seen in some of our patients, certainly require venesection.[15]

Although the previous randomized controlled trial, venesection, and low-dose antimalarial drugs demonstrated comparable efficacy, in our study, none of the five patients in our venesection-only group achieved biochemical remission. However, all exhibited clinical and biochemical improvement. It is worth mentioning that three of the five patients in this group were lost to follow-up after experiencing clinical improvement. Furthermore, the median follow-up time in this group was much shorter than in the other two groups (19 months compared to 34.5–119 months; $P = 0.033$). This shorter follow-up duration might hinder our ability to observe potential biochemical remission in the venesection-alone group.

Low, rather than high-dose antimalarial should always be prescribed in PCT, as high-dose chloroquine is known to be hepatotoxic in porphyria patients.[16] Furthermore, low-dose chloroquine was previously demonstrated to improve histopathological changes of liver damage in patients with PCT.[17] In our study, we prescribed low-dose antimalarial monotherapy only in patients with average baseline ALT values due to concerns about hepatotoxicity. However, low-dose antimalarials can be used cautiously in patients with PCT who have baseline ALT abnormalities. No hepatotoxicity side effects were reported in our study, both in those receiving antimalarial monotherapy and when combined with venesection, so including patients with normal and abnormal baseline ALT values.

The data derived from our study indicate that there was no significant difference in time to biochemical improvement between the three treatment groups. However, patients received individualized treatment based on the disease's severity, comorbidities, laboratory findings, and the likelihood and ease of attending the hospital. Patients with severe disease typically received a combined treatment approach with both venesection and antimalarial, as evidenced by those in the combined treatment group having a higher median ferritin level. Consequently, the efficacy of each treatment could not be directly compared, as it could have been if in a prospective randomized controlled trial, which was a limitation of our study. Another study limitation arises in the combined treatment group, where patients may have initiated one treatment before another rather than concurrently. Given the retrospective nature of the study conducted in a real-life setting, the median time to achieve biochemical improvement or remission may not entirely reflect the efficacy of the combined treatment.

Porphyrins are known liver carcinogens.[15] A previous study from Denmark and Sweden showed that PCT patients have an increased overall risk of cancer, primarily liver cancer, followed by lung cancer.[18] In our study, two patients had lung cancer, and one patient had liver cancer. In total, six of 27 patients (22%) had cancer, which appears to be notably higher compared to the prevalence of cancer in the UK population (1.5–2.5%).[19] However, our cohort had high rates of heavy alcohol intake and smoking, which were confounding factors. Consequently, a well-matched controlled prospective study is needed to

determine cancer risk in Scottish patients with PCT. However, there is sufficient concern to recommend that alpha-fetoprotein, liver ultrasound, and chest X-ray should be periodically requested in patients with PCT during their management and follow-up.

In conclusion, we have characterized PCT in Scottish patients and have shown that heavy alcohol intake and hemochromatosis are the leading underlying associated factors, with there often being combined precipitants. We recommend that the management of PCT should be individualized and that long-term follow-up is needed to monitor for disease relapse, but also with respect to cancer screening, particularly with liver and lung cancer in mind. Photoprotection to visible light, protecting skin from trauma, and management of precipitating causes and co-existing liver disease remain necessary management measures. Combination treatment approaches are often needed, particularly in those with severe disease. Further prospective studies of therapeutic strategies in PCT are required in order to optimize the management of patients with this challenging, rare disease.

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Data availability statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

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