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Porphyria Cutanea Tarda (PCT) experience in Victoria, Australia: A case series and literature review

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RESEARCH

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ABSTRACT

Background

Porphyria Cutanea Tarda (PCT) is a metabolic disorder resulting from a deficiency of hepatic enzyme uroporphyrinogen decarboxylase (UROD). UROD deficiency results in the accumulation of porphyrins, which are phototoxic and hepatotoxic. PCT patients are at increased risk of developing hepatocellular carcinoma.

Aims

We aim to describe a series of PCT patients presenting to a tertiary center over 35-year period from the 1980s to December 2015 and review current literature to date on PCT, with a focus on PCT management.

Methods

A search of the center's dermatology department and biochemistry database were performed to identify patients diagnosed with PCT. Demographic data, underlying risk factors and management details were obtained. Statistical tests were performed to identify any possible association between the variables of interest.

Results

34 patients were included in this study. Mean age of diagnosis was 48 years and there was no gender difference. 12 patients had Hepatitis C infection, 25 had excessive alcohol consumption, 13 had hereditary haemochromatosis. Eight patients developed oestrogen-associated or hormonal replacement therapy (HRT) induced PCT. 33 patients (97 per cent) responded to venesection. Six (18 per cent) patients were prescribed hydroxychloroquine, either alone or concurrently with venesection. They all achieved remission. Average duration of follow up is 13 years. One patient developed hepatocellular carcinoma (HCC).

Conclusion

Our study has reinforced venesection as an effective treatment for PCT. Low dose hydroxychloroquine can be used in patients where venesection is contraindicated or not tolerated. General measures such as alcohol abstinence, visible violet light protection and trauma avoidance are recommended.

Key Words

Porphyria Cutanea Tarda (PCT), uroporphyrinogen decarboxylase (UROD), venesection, hydroxychloroquine, heptatocellular carcinoma

What this study adds:

1. What is known about this subject?

PCT is a rare metabolic disorder. It is associated with increased risk of developing hepatocellular carcinoma. Limited data on PCT is currently available.

2. What new information is offered in this study?

New data on risk profiles, demographic and management details of PCT patients in Victoria and detailed review of current PCT literature are provided.

3. What are the implications for research, policy, or practice?

Larger study of PCT is warranted to provide greater understanding of this rare disease, especially in the era of new hepatitis C treatments.

Background

Porphyria Cutanea Tarda (PCT) is a metabolic disorder usually resulting from a deficiency of hepatic enzyme uroporphyrinogen decarboxylase (UROD), the fifth enzyme in the heme biosynthesis pathway.[1] Its peak incidence is in the fourth or fifth decades of life. Incidence is estimated to be 1:10000 to 1:25000 with equal gender ratio.[2,3] Liver dysfunction with hepatic iron overload causes reduction in UROD enzyme activity. This leads to accumulation of uroporphyrins and other highly carboxylated porphyrins in various organs especially liver and skin. They circulate in plasma and are excreted in urine and faeces.[4,5] The underlying liver disorder, plus the fact the porphyrins are hepatotoxic, result in an increased risk of developing hepatocellular carcinoma.[6-8]

There are two types of PCT: Type 1 (sporadic PCT) accounts for 75 per cent to 80 per cent of cases and Type 2 (familial PCT) accounts for 15 per cent to 20 per cent of cases.[1] PCT can be precipitated by multiple risk factors such as alcohol, oestrogens, viral hepatitis, conditions that lead to iron overload such as hereditary hemochromatosis and haemodialysis.[9] PCT has also been found to be associated with other conditions including diabetes mellitus, systemic or discoid lupus erythematosus, hepatic tumours, myeloproliferative and lymphoproliferative disorders.[5] Due to the rarity of the condition, there is currently limited literature on PCT and there has been no case series of PCT in Victoria, Australia to date.

Royal Melbourne Hospital is the main tertiary referral centre for porphyria in Victoria with its statewide referral service, multidisciplinary clinic and reference laboratory. Since the 1980s, more than one hundred cases of PCT have been seen here. Therefore, we aim to describe a series of PCT cases presenting to Royal Melbourne Hospital (RMH), review current PCT literature and provide recommendations on management.

Method

This research project has been approved by the Research and Ethics Committee of the Royal Melbourne Hospital (RMH). Patients were identified from RMH dermatology department and chemistry database. The diagnosis of PCT was made based on presence of characteristic skin findings including photo-distributed bullae and erosions, and confirmed by demonstration of elevated concentration of total plasma uroporphyrin, urine heptacarboxylic porphyrin and faecal isocoproporphyrin. Screening for hepatitis B and C, human immunodeficiency virus (HIV), hemochromatosis gene mutations (C282Y and H63D mutation) and iron studies were performed to identify potential precipitating factors. Each patient's demographic data and relevant history was obtained, including family history of PCT, alcohol consumption, medicinal oestrogen, and management details.

Results

One hundred and two PCT cases were identified at the initial search of RMH chemistry database from the 1980s to December 2015. However, the medical records of two thirds of the patients, who presented from 1980 to 1985, were no longer accessible or were excluded from the project due to loss to follow up and insufficient clinical data available. In total, 34 patients were included in this study. Statistical analysis was performed using Strata/IC Version 13.1 (College Station, TXT, USA) with two-tailed p-value <0.05 considered statistically significant.

The mean age of PCT diagnosis is 48 years of age (ranges from 21–84 years of age), with approximately equal male to female ratio (53 per cent (18 of 34) males versus 47 per cent (16 of 34) females). Linear regression statistical tests were used to analyse if there is any association between age of diagnosis and precipitating factors. In the univariate model, there were significant associations between earlier age of presentation and the use of oral contraceptive pill (β=-5.68, 95 per cent CI:-29.59, -1.76, p=0.028), presence of homozygous C282Y (β=-20.00, 95 per cent CI:-37.87, -2.13, p=0.029) or presence of any genetic mutation of either H63D or C282Y (β=-11.04, 95 per cent CI:-21.23, -0.84, p=0.035) (Table 1). However, in the multivariate analysis, there was no significant association found between age of presentation and risk factors (Table 1).

Increased skin fragility, characteristic tense bullae and erosions on sun-exposed sites such as dorsum of hands and forearms, face, scalp, chest and feet were typical clinical features observed in our patients. Four patients presented with hypertrichosis. Twenty four of 34 (70 per cent) of the patients had no family history of PCT. Only 18 per cent (6 of 34) had been formally diagnosed with familial PCT on genetic testing. Four other patients (11 per cent) had family

members with clinical suspicion of PCT but without formal diagnosis.

The most common precipitating factors found among our patients were as follows: 73.5 per cent (25 of 34) consumed excess alcohol, 38 per cent (13 of 34) had hemochromatosis, 38 per cent (13 of 34) had, hepatitis C and 20 per cent (7 of 34) used OCP or HRT (20 per cent). One third of our patients (11 of 34) had only one precipitating factors, however, the majority (70 per cent) (23 of 34) had more than one precipitating factor identified (Table 2). Logistic regression analysis revealed that patients with C282Y mutations were less likely to consume alcohol in univariate model (OR 0.3, 95 per cent CI:0.09, 0.99). However, this association was not significant (OR=0.19, 95 per cent CI:0.04, 1.03) when adjusted for age and sex (Table 3). Hepatitis infection (Hepatitis B and C) was diagnosed in 13 patients (38 per cent), 11 of which were diagnosed in male patients. Hereditary hemochromatosis was present in 38 per cent of patients (13 of 34)) and 24 per cent of patients (8 of 34) developed oestrogen or HRT-induced PCT.

General measures of sun avoidance, sunlight protection, abstinence from alcohol and cessation of medicinal oestrogens are recommended to all of our patients. Venesection was prescribed in 33 patients (97 per cent). Only one patient did not receive venesection due to pre-existing anaemia. The median numbers of venesections required was 9 (IQR=6-14). Statistical analysis did not reveal any significant differences in the number of venesections stratified by risk factors. Three patients (9 per cent) required more than 20 venesections due to ongoing alcohol consumption.

Six (18 per cent) patients were prescribed hydroxychloroquine. Three (9 per cent) received hydroxychloroquine only due to pre-existing anaemia or acquired anaemia post venesection. Concurrent venesection and hydroxychloroquine were prescribed in the remaining three patients (9 per cent), two due to inadequate symptom control with venesection only, and one was for treatment of hemochromatosis. All patients (100 per cent) who received hydroxychloroquine achieved remission.

Of the 12 patients with a history of Hepatitis C, only three were treated successfully with antiviral therapies. Two failed to respond and seven did not receive treatment. This was prior to the availability of the direct acting antivirals. The average follow-up period is 13 years (ranges from 0 to 40 years). One of 34 patients, who failed to respond to Hepatitis C treatment, developed hepatocellular carcinoma after nine years of hepatitis C diagnosis and was treated with radiotherapy.

Discussion

Porphyrias refer to eight genetically distinct metabolic disorders resulting from different heme-biosynthesis pathway enzyme deficiency.[9] These conditions are mostly genetic autosomal dominant, autosomal recessive or X-linked with the exception of porphyria cutanea tarda where most presentations are acquired.[10] This complex and multifactorial disorder exists in two main forms: type 1 (sporadic) and type 2 (familial) and expresses clinically only when hepatic UROD activity is diminished to less than 30 per cent.[1,11] The estimated prevalence of PCT is between 1:10000 to 1:25000. It occurs mainly in the fourth or fifth decade of life and with approximately equal male to female ratio.[2,3]

Our PCT patients presented with typical clinical features. None of our patients presented with scarring alopecia or sclerodermoid plaques. Perhaps this is due to the improvement in disease recognition and prompt treatment initiation, similar to findings reported by Munoz-Satos et al.[12]

Evidence of genetic mutations in HFE locus (C282Y and/or H63D) were confirmed in 38 per cent (13 of 34) of our patients with mean age of presentation at 41 years of age in comparison with 52 years of age in patients without hereditary hemochromatosis. However, this difference does not reach statistical significance (Table 1).

Among precipitating factors, alcohol has long been recognized as a major risk factor for the development of PCT.[13] It is theorized that ethanol is a UROD inhibitor and an inducer of early enzymes in heme biosynthesis pathway.[14] Moreover, chronic alcoholism inhibits erythropoiesis, increases dietary iron absorption and further precipitates iron overload. Sampietro et al. suggested that chronic alcoholism may be associated with the inheritance of HFE mutation.[15] However, in our study, there was no significant association demonstrated between alcohol consumption and HFE mutation. This is similar to outcome reported by Vieiria et al.[16] In a study by Lauret et al., it was suggested that the risk of developing HCC is higher in patients who have alcoholic cirrhosis and are carrier of C282Y mutations.[17]

A strong correlation of hepatitis C infection in sporadic PCT has been demonstrated in multiple studies. This was first

reported by Fargion et al. in 1992, where 75 per cent of the PCT patients were diagnosed with Hepatitis C infection.[18] A systematic review of over 2000 PCT cases by Gisbert et al. revealed the overall 50 per cent HCV prevalence among PCT patients,[19] however, the reverse was not true.[20] HCV prevalence also varies significantly by geographic distribution with the lowest prevalence observed in Australia to be 25 per cent of PCT patients.[5] A comprehensive assessment of liver function and screening for HCV is therefore essential in PCT workup. In our series, prevalence of HCV among sporadic PCT is 42 per cent (nine patients). The exact mechanism of how HCV precipitates PCT is unknown. It is proposed that chronic HCV infection causes a reduction of glutathione in hepatocytes. This leads to impaired ability to reduce oxidized uroporphyrins, which accumulates and inhibits UROD activity.[21]

The fourth known trigger of PCT is oestrogen therapy such as oral contraceptives, hormonal replacement therapy or tamoxifen for the treatment of breast cancer. In our series, oestrogen therapy was identified as one of the precipitating factors in eight patients, and hormone replacement therapy in two patients. It is proposed that enhanced free radical formation from oestrogen quinone acts as a possible culprit in precipitating PCT.[22]

Other conditions such as diabetes mellitus, systemic lupus erythematous, dermatomyositis, haematological malignancy, sideroblastic anaemia and thalassaemia have been reported to be associated with PCT.[9]

Hepatocellular carcinoma is recognized as a life-threatening complication of PCT. This is caused by multiple factors such as history of chronic alcoholism, hepatitis C infection and the effects of accumulative hepatotoxic porphyrins in PCT.[9] It is reported that around 15 per cent of PCT patients develop hepatocellular carcinoma a decade after presentation, of which major contributing risks identified are the duration of symptomatic period prior to initiation of treatment and male gender.[9] In our series, one patient developed hepatocellular carcinoma after nine years of clinical diagnosis of Hepatitis C.

Avoidance of sunlight, cessation of alcohol and cessation medicinal oestrogen are non-medical therapies recommended in all patients diagnosed with PCT.[9] However, the mainstay of PCT treatment is venesection, especially in patients with HFE-mutation hemochromatosis. Patients with hereditary hemochromatosis excessively absorb iron via gastrointestinal mucosa. Therefore, regular monitoring of serum ferritin levels and frequent venesections to prevent end-organ damage are extremely important.[23]

Venesection is often initiated at four-weekly intervals and tailored according to biochemistry profiles and patient response. Studies have demonstrated a reduction in blisters within two to three months of venesection, and improvement in skin fragility by nine months.[9] Ninety seven per cent of our cases responded to venesection. The median number of venesections required was 9 (IQR=6-14). There is no significant difference in the number of venesections stratified by precipitating factors (Table 3). Due to the differences in timing of reviews and severity of diseases among our cases, it was difficult to compare the degree of improvement in clinical features following venesections among cases. It was noted by Grossman et al. that hypertrichosis and sclerodermoid plaques respond more slowly following treatment initiation.[24] In our cohort, only two patients relapsed but achieved remission after re-commencement of treatment (Table 2).

Low dose chloroquine is an effective treatment for PCT, which often leads to resolution of blisters and fragility within six months of initiation.[9] Chloroquine is no longer readily available in Australia. Low dose hydroxychloroquine (200mg twice per week) has been used to treat PCT successfully. It is shown to be safe, cheap and as effective as venesection.[25] However, antimalarials do not reduce the iron overload, therefore, patients with homozygous or heterozygous HFE mutations and those with high serum ferritin levels, iron depletion through venesection is preferable.[9]

In PCT patients with HCV infection, antiviral treatment may improve the clinical manifestations of PCT, especially when it was preceded by venesection.[26] Iron overload is associated with progression of HCV liver disease, therefore, depletion of iron stores by venesection is beneficial for both PCT and HCV. Fernandez et al. demonstrated that the presence of PCT results in the failure of interferon (IFN)-based regimens in the treatment of HCV infection.[26] Therefore, effective PCT treatment with vensection should precede IFN-based regimens. Hepatitis C was successfully treated in three of our patients, two failed to respond to IFN-based regimens and seven were not treated. In 2014, three new direct-acting antivirals (DAAs) have been licensed as IFN-free regimens for the treatment of HCV infection worldwide.[26] In Australia, DAAs have been made available without restriction to patients since 2016. In a very recent study by Sood et al., authors reported a significant reduction in ferritin and uroporphyrin levels in eight PCT

patients, who were cured of Hepatitis C with DAAs.[27] Authors, suggested that DAAs probably offer curative benefits for HCV positive PCT patients. Further studies are warranted to examine the impact of Hepatitis C treatment on PCT patient population.

Conclusion

In conclusion, to our knowledge, this is the first case series of PCT in Victoria, Australia. Due to the limited access to patients' histories and rarity of the condition, our study numbers remain small, however, it has successfully reinforced the clinical presentations, age of onset and precipitating factors associated with PCT. Venesection has been shown to be an effective first-line treatment for PCT. Low dose hydroxychloroquine can be used in patients who are contraindicated to or intolerant of venesection. Further and larger studies are needed to provide greater understanding of PCT, especially in the era of new hepatitis C treatments.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

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Table 1: Associations between age of diagnoses and precipitating factors

Cause	Univariable model		Multivariable model[a]		Multivariable model[b]	
	Difference	**95% CI**	**Difference**	**95% CI**	**Difference**	**95% CI**
ETOH						
Absent	Reference		Reference		Reference	
Present	-0.34	-12.39,11.71	-3.75	-16.08,8.58	-3.18	-15.08,8.71
HRT						
Absent	Reference		Reference		Reference	
Present	11.37	-6.93,29.66	6.05	-12.30,24.40	5.91	-12.25,24.07
OCP						
Absent	Reference		Reference		Reference	
Present	**-15.68**	**-29.59,-1.76**	-12.74	-27.16,1.69	-14.62	-29.53,0.30
Hepatitis B						
Absent	Reference		Reference		Reference	
Present	3.12	-28.33,34.57	-9.03	-39.28,21.22	-7.02	-38.32,24.29
Hepatitis C						
Absent	Reference		Reference		Reference	
Present	48.91	42.32,55.50	-8.24	-19.53,3.05	-6.77	-18.49,4.94
C282Y						
Per allele increase	**-7.81**	**-15.60,-0.03**	-8.28	-16.76,0.20		
H63H						
Per allele increase	-7.83	-16.09,0.44	-7.87	-15.97,0.23		
Any mutation						
Absent	Reference				Reference	
Present	**-11.04**	**-21.23,-0.84**			-10.42	-21.31,0.47

[a] Adjusted for ETOH, HRT, OCP, HepB, HepC, number of C282yY alleles and number of H63D alleles
[b] Adjusted for ETOH, HRT, OCP, HepB, HepC and any mutation

Table 2: Demographic, precipitating factors and treatment details of our patients

Patient	Age	Sex	Age of diagnosis	Precipitating factors	Family history	Venesections	Other treatments/Comments	Relapse times/Comments
1	60	M	48	ETOH, Hep C	Nil	6	Nil Hep C treatment	0
2	34	F	25	ETOH, heterozygous C282Y/H63D, OCP	Nil	6	Implanon cessation, Betamethasone 0.5mg/g ointment	0
3	74	M	66	ETOH, Hep C	Nil	4	Hep C treatment Hydroxychloroquine 200mg 2x/week (commenced due to symptomatic anaemia secondary to venesections)	0
4	58	M	55	ETOH	Yes	8	Nil	0
5	52	F	49	ETOH, homozygous H63D, HRT	Nil	6	HRT cessation, restarted due to hot flushes without precipitating PCT	0
6	60	F	49	Hep C, heterozygous C282Y	Nil	5	Nil Hep C treatment	0
7	59	M	39	ETOH, Hep C	Nil	5	Nil Hep C treatment Concurrent hydroxychloroquine 200mg (commenced due to ongoing symptoms with venesection only) Methylprednisolone aceponate 1mg/g Vitamin D 1000IU.	0
8	57	M	54	ETOH, Hep C	Nil	7	Hep C treatment, Betamethasone 0.5mg/g ointment PRN	0
9	68	M	66	ETOH, heterozygous C282Y	Nil	12	Nil	0
10	73	F	72	ETOH	Nil	9	Concurrent hydroxychloroquine 200mg 2x/week (commenced due to ongoing symptoms with venesection only)	0
11	67	M	65	ETOH	Nil	23 (non-compliant with ETOH cessation)	Nil	0
12	40	F	23	ETOH, OCP	Yes	4	Lower dose estrogen OCP	0
13	39	F	38	ETOH, homozyous H63D, OCP	Yes	7	OCP ceased, Betamethasone 0.5mg/g ointment	0
14	59	M	25	ETOH, homozygous H63D	Nil	11 (5+2+4)	Hydrocortisone Patient developed first flare after 5 years in remission, 2nd flare after 8 years in remission. Both due to ETOH consumption	2 (ETOH trigger)
15	51	M	44	ETOH, Hep C	Suspicion	12	Failed Hep C treatment	0
16	56	M	46	Hep C	Nil	18	Nil Hep C treatment	0

17	74	F	69	ETOH, HRT	Suspicion	7	HRT cessation, Methylprednisolone aceponate 1mg/g	0
18	52	M	49	ETOH	Nil	25 (non-compliant with ETOH cessation)	Nil	0
19	59	M	48	ETOH, Hep C, heterozygous C282Y	Suspicion	20	Hep C treatment	0
20	44	F	41	Homozygous C282Y	Yes	15	Methotrexate 15mg daily Concurrent hydroxychloroquine 200mg three times/week (commenced for treatment of PCT and systemic lupus erythematosus)	0
21	84	F	84	ETOH	Nil	0	Hydroxychloroquine 200mg twice/week (Nil venesection due to pre-existing anaemia)	0
22	66	F	60	Heterozygous C282Y	Nil	0	Tacrolimus cream	0
23	23	F	21	Homozygous C282Y	Nil	5	Nil	0
24	92	F	57	HRT	Nil	16	HRT cessation	0
25	53	M	42	ETOH, Hep C	Nil	9	Nil Hep C treatment	0
26	98	F	58	HRT	Suspicion	5	Nil	0
27	67	M	51	Hep C, heterozygous H63D/C282Y	Yes	14	Failed Hep C treatment, Betamethasone 0.5mg/g ointment	0
28	43	F	29	ETOH, homozygous C282Y, OCP	Yes	10	OCP cessation	0
29	68	F	33	ETOH, heterozygous H63D/C282Y	Nil	4	Nil	0
30	85	M	55	ETOH	Nil	6	Nil	0
31	57	M	34	ETOH, Hep C	Nil	15	Nil Hep C treatment, Betamethasone 0.5mg/g ointment	0
32	82	M	51	ETOH	Nil	13	Nil	0
33	66	F	51	Hep B	Nil	12	Nil	0
34	66	M	34	ETOH, Hep C	Nil	31 (15+16)	Nil Hep C treatment Hydroxychloroquine 200mg twice/week (Commenced to due to symptomatic anaemia secondary to venesections) Patient developed flare of PCT after 5 years in remission	1 (uncertain trigger)

Table 3: Associations between numbers of venesections stratified by risk factors

Cause	Univariable model		Multivariable model[a]		Multivariable model[b]	
	IRR	95% CI	IRR	95% CI	IRR	95% CI
ETOH						
Absent	1.00		1.00		1.00	
Present	0.51	0.22,1.16	0.56	0.19,1.64	0.47	0.18,1.21
HRT						
Absent	1.00		1.00		1.00	
Present	1.26	0.36,4.42	1.17	0.31,4.40	0.86	0.25,3.01
OCP						
Absent	1.00		1.00		1.00	
Present	0.72	0.23,2.24	1.19	0.27,5.33	0.97	0.26,3.57
Hepatitis B						
Absent	1.00		1.00			
Present	2.77	0.36,21.33	1.44	0.16,13.18	1.07	0.12,9.16
Hepatitis C						
Absent	1.00		1.00			
Present	0.52	0.25,1.08	0.56	0.25,1.26	0.51	0.23,1.13
C282Y						
Per allele increase	1.26	0.76,2.10	0.99	0.51,1.95		
H63H						
Per allele increase	0.67	0.37,1.20	0.63	0.31,1.28		
Any mutation						
Absent	1.00				1.00	
Present	0.98	0.45,2.12			0.65	0.26,1.58

IRR = incident rate ratio – number of phlebotomies per active year
CI = confidence interval
[a] Adjusted for ETOH, HRT, OCP, HepB, HepC, number of C282yY alleles and number of H63D alleles
[b] Adjusted for ETOH, HRT, OCP, HepB, HepC and any mutation