# The role of inherited and acquired factors in the development of porphyria cutanea tarda in the Argentinean population

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***Background:*** Inherited and environmental factors are implicated in the expression of porphyria cutanea tarda (PCT); the contribution of each factor depends on the population.

***Objective:*** To provide a review of PCT cases diagnosed in Argentina over 24 years and evaluate the role of different precipitating factors in its pathogenesis.

***Methods:*** Plasma and urinary porphyrin levels and erythrocyte uroporphyrinogen decarboxylase (URO-D) activity were determined. Potential precipitating factors were identified in each patient. Additional tests for hepatitis C virus (HCV) and hemochromatosis gene mutations were carried out.

***Results:*** Several factors (mainly alcohol abuse in men and estrogen ingestion in women), alone or combined were identified in our patients. Prevalence of HCV infection was 35.2%. Inherited URO-D deficiency occurs in 25.0% of cases. H63D was the most common hemochromatosis gene mutation. High incidence of PCT associated with HIV infection was found.

***Conclusions:*** PCT is multifactorial. Therefore, knowledge of all risk factors in each patient is important for the management of the disease. (J Am Acad Dermatol 2005;52:417-24.)

Porphyria cutanea tarda (PCT) is the most common porphyria, more frequent in men than in women with a prevalence ranging from 1:5,000 to 1:25,000 people.[1] The disease usually occurs in adult life and it is characterized by skin photosensitivity with blistering on sun-exposed areas, skin fragility, hyperpigmentation, and hypertrichosis.[1] Biochemically, it is characterized by high levels of porphyrins, principally uroporphyrin, in plasma and urine.[1] PCT is caused by subnormal activity of uroporphyrinogen decarboxylase (URO-D, enzyme classification [EC] 4.1.1.37), the fifth enzyme in the heme biosynthetic pathway. URO-D catalyzes the conversion of uroporphyrinogen III to coproporphyrinogen III by the sequential removal of the 4 carboxylic groups of the acetic acid side chains.[2]

There are two main forms of PCT: type I (sporadic) and type II (familial, autosomal dominant).[1,3]

*Abbreviations used:*

| | |
|---|---|
| ALA: | 5-aminolevulinic acid |
| EC: | enzyme classification |
| EDTA: | ethylenediamine tetraacetic acid |
| HBV: | hepatitis B virus |
| HCV: | hepatitis C virus |
| HFE: | hemochromatosis gene |
| PCR: | polymerase chain reaction |
| PCT: | porphyria cutanea tarda |
| RBC: | red blood cells |
| RT-PCR: | reverse transcriptase—polymerase chain reaction |
| SD: | standard deviation |
| URO-D: | uroporphyrinogen decarboxylase |

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Type II PCT is transmitted as a dominant trait with low penetrance, and the enzyme activity is reduced to approximately 50% of normal in all tissues. It is caused by heterozygocity for mutations in the URO-D gene. Type I PCT is the most common PCT type and subnormal URO-D activity is restricted to the liver; for this reason, both type I and type II PCT can be differentiated by erythrocyte URO-D activity values.[4] No mutations have been found in the URO-D gene in type I PCT, and the presence of a liver-specific inhibitor of the enzyme has been considered.[5] There is also a form of familial PCT called type III, in which a family history of PCT is observed, but subnormal URO-D activity is restricted to the liver.[6,7] Moreover, URO-D mutations in homozygosis or in compound heterozygosis, cause a more severe form of hereditary PCT, called hepatoerythropoietic porphyria, which has an early clinical onset with a markedly reduced URO-D activity in all tissues (3%-27% of normal in erythrocytes) and a phenotype similar to that of congenital erythropoietic porphyria.[1,8]

The clinical manifestation of PCT is frequently associated with exposure to precipitating agents, including polyhalogenated aromatic hydrocarbons (such as hexachlorobenzene and dioxin), alcohol abuse, estrogen ingestion, iron overload, and infection with hepatitis C virus (HCV) and, less frequently, hepatitis B virus (HBV).[1,9] All of these factors cause liver dysfunction, a common sign in PCT patients.[1]

PCT associated with HIV infection has also been reported.[10,11] However, the role of HIV in the pathogenesis of PCT is not yet clear, since in most PCT-HIV patients, other risk factors were also observed.[11,12]

It is well known that mild to moderate hepatic iron overload plays a key role in the pathogenesis of PCT. Although it is now accepted that iron does not directly inhibit URO-D, it is known that it is required for its inactivation.[13] The causes of iron overload appear to be heterogeneous. An impaired iron metabolism, and therefore, altered iron status, may be secondary to exogenous factors such as alcohol and diet.[14,15] In patients with chronic viral hepatitis (HBV and HCV), increased deposition of iron in the liver is observed.[16] However, hemochromatosis is the most common cause of primary iron overload.[17,18] Mutations C282Y and H63D in the hemochromatosis gene (HFE),[19] associated with hereditary hemochromatosis, have been found to be more frequent in PCT than in control populations.[20-22]

A specific class of cytochrome P450 enzymes catalyzes the oxidation of uroporphyrinogen to uroporphyrin and it has been proposed that URO-D inactivation may be caused by an inhibitor generated during this process.[1,23] Thus, a deficiency in the levels of antioxidants, such as vitamin C, may also constitute a risk factor in PCT development.[1]

Association of PCT with other pathologies, such as diabetes,[24] lupus,[25] leukemia,[26] and Hansen's disease[27] has been reported. Moreover, cases of PCT linked with the treatments used for other pathologies, such as estrogen therapy for prostate cancer[28] and hemodialysis in patients with renal failure,[29] were also observed.

## MATERIALS AND METHODS

### Patients and PCT diagnosis

From March 1977 to November 2000, 2099 patients were referred to the National Research Institute on Porphyrins and Porphyrias from different Argentinean health centers with presumed PCT diagnosis based on clinical symptoms. Routine biochemical laboratory tests were performed following the methodology described by Batlle.[30] Fresh 24-hour urine samples and peripheral blood samples were collected from each patient for diagnostic purposes. Plasma porphyrin content was determined fluorometrically and urinary porphyrin levels were measured spectrophotometrically after their separation from urine by ion exchange chromatography. The porphyrins excretion pattern was obtained by thin layer chromatography. Patients gave their informed consent to participate in this epidemiologic study of PCT.

Patients were asked about the onset date of the cutaneous photosensitivity, family history of the disease or symptomatology, alcohol intake (>60 g/day for more than 5 years), estrogen use, exposure to chemicals including polyhalogenated compounds (such as hexachlorobenzene and dioxin), viral infections (HCV, HBV, and HIV), and other pathologies and their treatments. The clinical records from the referring health centers were also taken into account. To estimate the frequency of type II PCT, URO-D activity was measured in red blood cells (RBC) in a randomly selected group of 124 unrelated patients, 31 females and 93 males, between the ages of 7 and 74 years. Additional standard tests for HCV infection were carried out also after obtaining the express consent from patients. Furthermore, the presence of HFE mutations was studied in both type I and type II PCT patients.

### URO-D activity

Heparine-blood samples were obtained by venous puncture. Erythrocytes were then separated by centrifugation, lysed by freeze-thawing in the presence of Triton X 100 5% (0.2 mL/mL erythrocytes) and diluted 3 times in sodium phosphate buffer 67 mM pH 7. Uroporphyrinogen III was used as substrate after reduction of 50 $\mu$g/mL uroporphyrin III

(Porphyrin Products Inc, Logan, Utah) in 25 mM NaOH with 3% sodium amalgam. A constant amount of protein and uroporphyrinogen was added to each incubation mixture. URO-D activity was measured in the hemolysate in 3 mL final volume that contained 2 mM reduced glutathione, 0.1 mM EDTA, 67 mM sodium phosphate buffer at pH 7 and 4 $\mu$M uroporphyrinogen III. The reaction mixture was incubated at 37°C for 60 minutes in the dark and in anaerobiosis (under nitrogen); the reaction was stopped with a mixture of TCA 50%: dimethylsulphoxide (1:1), to a final TCA concentration of 5% in the incubation mixture. The porphyrinogens were oxidized to porphyrins by white light illumination for 20 minutes. After centrifugation, the samples were filtered through 0.2 $\mu$M Whatman filters and analyzed by high pressure liquid chromatography with fluorescence detection in accordance with the method of Lim et al.[31] The nanomoles of coproporphyrin III produced were determined by extrapolation from a calibration curve of nanomoles of coproporphyrin III vs peak area. One unit of URO-D activity was defined as 1 nmol of coproporphyrin III produced per mL RBC at 37°C per hour. Any patient having an erythrocyte URO-D activity value 50% of normal (mean value of 50 healthy donors) was considered as a type II PCT case.

### HCV infection

In 108 PCT patients, serum was tested for anti-HCV (EIA, Abbott Laboratories, Chicago, Ill). Anti-HCV was tested by a second-generation enzyme-linked immunosorbent assay, and the anti-HCV positive sera were subjected to reverse transcription followed by nested polymerase chain reaction (RT-nested PCR) for detection of HCV RNA, as described elsewhere.[32]

### HFE mutations

In order to detect mutations in the HFE gene in PCT patients, 10 type I and 20 type II PCT patients were studied. Genomic DNA was extracted from EDTA-collected blood samples and analyzed for the common HFE mutations (H63D, S65C, and C282Y) by PCR and direct sequencing employing the Amplicycle Sequencing Kit (Applied Biosystems; Roche Molecular Systems, Brandburg, NJ). PCR was performed using two sets of primers for amplification of exons 2 and 4 in the HFE gene, and the purified products were sequenced employing the primers used for PCR reactions.

### Statistical analysis

Data were analyzed using the Student *t* test to compare means, and the chi-square test was used to estimate differences in proportions.

## RESULTS

### Frequency and onset age

PCT was confirmed by biochemical determinations in 47.6% of the 2099 presumed PCT patients. Biochemical diagnosis was based on an increased urinary excretion of porphyrins and increased plasma porphyrins content with a fluorescence emission maximum at 618 nm. Urporphyrin and heptaporphyrin were the main urinary porphyrins in thin-layer chromatography. From the 1000 individuals diagnosed with this disease, the prevalence of PCT has been calculated as 1:36,000, considering the number of patients received in our insitiute during the 24-year period and the total country population at the end of the period (census year 2001). However, we should note that, although our institute is the reference center for porphyrias in Latin America, the possibility exists that some patients may not have come to us for diagnosing, which would result in a lower number of prevalence. Also, if we consider the census of 1980 and the census of 1991, the prevalence would be increased to 1:32,000.

Of all these true PCT patients, 797 were men and 203 were women, so that the man-woman ratio was about 4:1. It should be noted that the 1,000 PCT patients come from 954 different families, 32 of which include more than one symptomatic member (23 families with 2 cases, and 9 families with between 3 and 5 cases each).

As regards to the age at onset, about 70% of the patients developed clinical symptoms when they were over 40 years old, with greater frequency between age 41 and 60 (51.8%). However, there are some cases in which the clinical symptoms appeared between age 19 and 40 (27.8%), and before age 19 (2.6%), the latter being considered as a childhood onset (Table I). Moreover, in the whole PCT population, the onset age (mean ± standard deviation [SD]) was 47.6 ± 14.4 years and no significant differences were found between men and women. It should be noted that for infantile-PCT cases the man-woman ratio was different from the adult-PCT, being about 1:1 (12:14) ($P < .001$). These 26 infantile-PCT cases came from 25 families, 12 of which had more than one member with PCT (Table II).

### Precipitating factors and association with other pathologies

Data about known potential precipitating factors obtained from a patient questionnaire and from their clinical histories is shown in Table III. To evaluate the significance of each factor, patients were classified into adult-PCT (males and females), infantile-PCT, and HIV-positive patients. Alcohol abuse was the most important precipitating agent in men (51.3%),

**Table I.** Age at onset of cutaneous photosensitivity in PCT patients

| Age (y)* | Patients [N (%)] Total (N = 1,000) | Men (n = 797) | Women (n = 203) |
|---|---|---|---|
| Before 19 | 26 (2.6%) | 12 (1.5%) | 14 (6.9%) |
| 19-30 | 88 (8.8%) | 71 (8.9%) | 17 (8.4%) |
| 31-40 | 190 (19.0%) | 158 (19.8%) | 32 (15.8%) |
| 41-50 | 247 (24.7%) | 218 (27.4%) | 29 (14.3%) |
| 51-60 | 271 (27.1%) | 212 (26.6%) | 59 (29.0%) |
| After 60 | 178 (17.8%) | 126 (15.8%) | 52 (25.6%) |

*Age at which the clinical symptoms first appeared (mean ± SD) was 47.6 ± 14.4 years (median 48 years, range 3-89 years) for all PCT patients, being 47.4 ± 13.3 years (median 48 years, range 5-84 years) for men and 48.5 ± 18.1 (median 53 years, range 3-89 years) for women.

**Table II.** Families with infantile-PCT cases

| Family | Infantile-PCT cases [sex (age*)] | Number of adult-PCT relatives |
|---|---|---|
| 1 | M (11) F (7) | 2 |
| 2 | F (13) | 3 |
| 3 | F (7) | 2 |
| 4 | F (9) | 2 |
| 5 | M (11) | 2 |
| 6 | F (3) | 1 |
| 7 | M (5) | 1 |
| 8 | F (5) | 1 |
| 9 | F (7) | 1 |
| 10 | M (10) | 1 |
| 11 | F (10) | 1 |
| 12 | M (11) | 1 |
| 13 | F (3) | - |
| 14 | F (3) | - |
| 15 | F (6) | - |
| 16 | M (6) | - |
| 17 | F (6) | - |
| 18 | M (7) | - |
| 19 | M (9) | - |
| 20 | M (11) | - |
| 21 | M (12) | - |
| 22 | F (14) | - |
| 23 | F (16) | - |
| 24 | M (16) | - |
| 25 | M (18) | - |

*PCT*, Porphyria cutanea tarda.
*Ages indicated are for the onset of clinical symptoms.

but this percentage rose to 60.9% when the cases of high alcohol intake associated with other factors were also considered. In the women's group, estrogen ingestion was the prevalent developing agent (28.7%). It was also found that in both groups (10.3% of men and 7.9% of women), more than one factor could have been responsible for overt PCT. In children, exposure to polyhalogenated compounds was the main triggering factor (23.1%) and no other coexisting factors were found.

From 1989 to November 2000, we diagnosed 62 PCT patients infected with HIV (61 men and 1 woman), with an onset age between 20 and 50 years (median 34 years). As shown in Table III, other factors were also present in most cases: 46.8% were alcohol abusers and 20.9% were coinfected with hepatitis virus (HCV or HBV). In 25.8%, more than one factor was identified, mainly alcohol and HCV infection. It is noteworthy that an earlier onset age is observed in the PCT-HIV group than in the general PCT population, being 34.4 ± 6.4 years ($P < .001$).

The association of PCT with other pathologies was also observed, mainly diabetes mellitus, in 9% of our PCT patients. Minor cases were 3 patients with prostate cancer (under estrogen therapy); 3 with systemic erythematosus lupus; 4 with chronic myeloid leukemia (one of them was an infantile-PCT case); and 2 with Hansen's disease. We also found 9 hemodialized patients with overt PCT: 2 cases of infantile-PCT and 7 cases of adult-PCT (3 women and 4 men), all of them having developed PCT after 2 to 15 years of dialysis.

### Sporadic and familial PCT patients

Blood URO-D activity was measured in 124 unrelated patients. Results indicated that 31/124 (25.0%) of our PCT population had type II PCT. URO-D values (mean ± SD) for each PCT type were 1.78 ± 0.37 U $mL^{-1}$ RBC for type II and 3.98 ± 0.75 U $mL^{-1}$ RBC for type I, the control value being: 4.17 ± 0.60 U $mL^{-1}$ RBC. In two patients from families with more than one symptomatic member, blood URO-D activity was normal, so that they can be considered as having type III PCT. In the group studied (n = 124), 4 patients were infantile PCT cases and all of them were type II PCT. It has been noted that 11 patients were HIV positive, and only one of them was type II PCT. Moreover, the men-women ratio was significantly different in the two types of PCT, being about 5:1 (77:16) for type I and 1:1 (16:15) for type II ($P < .01$).

### HCV infection and HFE mutations

Infection with HCV was studied in 108 PCT patients (83 males and 25 females). Anti-HCV was found in 38 patients (33 males and 5 females), in all of them HCV RNA being detected by RT-PCR. Based on these results, the prevalence of HCV in the PCT population was 35.2%. This study showed a higher prevalence of HCV than that obtained from the clinical histories (Table III). Of these 38 HCV-positive patients, 24 (63.2%) were also alcohol abusers, and

**Table III.** Frequencies of precipitating factors in patients with PCT

| Precipitating factors[†] | Frequencies [N (%)][*] | | | | |
|---|---|---|---|---|---|
| | All patients (N = 1,000) | Adult-PCT males (n = 724) | Adult-PCT females (n = 188) | Infantile-PCT (n = 26) | HIV(+)PCT (n = 62) |
| Alcohol | 423 (42.3%) | 371 (51.3%) | 23 (12.2%) | - | 29 (46.8%) |
| Polyhalogenated | 82 (8.2%) | 62 (8.6%) | 14 (7.5%) | 6 (23.1%) | - |
| Estrogens | 61 (6.1%) | 6 (0.8%) | 54 (28.7%) | 1 (3.8%) | - |
| Iron | 8 (0.8%) | 5 (0.7%) | 2 (1.1%) | 1 (3.8%) | - |
| HBV | 8 (0.8%) | 2 (0.3%) | 1 (0.5%) | 2 (7.7%) | 3 (4.8%) |
| HCV | 23 (2.3%) | 9 (1.2%) | 4 (2.1%) | - | 10 (16.1%) |
| More than one | 106 (10.6%) | 75 (10.3%) | 15 (7.9%) | - | 16 (25.8%) |
| Alcohol + polyhalogenated | 40 (4.0%) | 39 (5.4%) | 1 (0.5%) | - | - |
| Alcohol + estrogens | 9 (0.9%) | 3 (0.4%) | 6 (3.2%) | - | - |
| Alcohol + iron | 2 (0.2%) | 2 (0.3%) | - | - | - |
| Alcohol + HBV | 4 (0.4%) | 3 (0.4%) | 1 (0.5%) | - | - |
| Alcohol + HCV | 37 (3.7%) | 21 (2.9%) | 2 (1.1%) | - | 14 (22.6%) |
| Polyhalogenated + HBV | 3 (0.3%) | 3 (0.4%) | - | - | - |
| Polyhalogenated + HCV | 4 (0.4%) | 2 (0.3%) | 2 (1.1%) | - | - |
| Estrogens + iron | 1 (0.1%) | - | 1 (0.5%) | - | - |
| Estrogens + HCV | 1 (0.1%) | - | 1 (0.5%) | - | - |
| Alcohol + polyhalogenated + HCV | 1 (0.1%) | 1 (0.1%) | - | - | - |
| Alcohol + estrogens + HCV | 1 (0.1%) | - | 1 (0.5%) | - | - |
| Alcohol + HCV + HBV | 3 (0.3%) | 1 (0.1%) | - | - | 2 (3.2%) |
| Not identified | 289 (28.9%) | 194 (26.8%) | 75 (40.0%) | 16 (61.6%) | 4 (6.5%) |

*HBV*, Hepatitis B virus; *HCV*, hepatitis C virus; *PCT*, porphyria cutanea tarda.
*Data were provided by the patients and by the clinical records from the health centers from which they were referred.
[†]Alcohol: Intake >60 g/day for more than 5 years; polyhalogenated compounds: exposure to hexachlorobenzene; estrogens: contraceptives use or estrogen therapies; iron: treatments for anaemia; HIV, HCV, and HBV: diagnosis made by the health centers from which patients were referred.

in 9 cases (23.7%) no other factor was coexisting with HCV infection. No significant differences were found for alcohol intake between positive and negative HCV patients. From the results of erythrocyte URO-D activity, the HCV prevalence by type of PCT was 38.0% for type I and 27.6% for type II.

In addition, the presence of common HFE mutations was studied in groups of sporadic and familial PCT patients. It was found that 9 out of 20 type II PCT (45.0%) and 7 out of 10 type I PCT (70.0%) were carriers of at least one mutated allele for one of the already-reported HFE mutations. C282Y mutation was found in only one patient with type II PCT who also carried the H63D mutation, being a compound heterozygous case. H63D mutation was found in the homozygous form in two patients with type II PCT and one patient with type I PCT. Six individuals with type I PCT and 6 with type II PCT carried the H63D mutation in the heterozygous form. No patient had the S65C mutation.

## DISCUSSION

PCT is the most common of all porphyrias in our country with a prevalence of 1:36,000, which is lower than that found in other populations studied.[1] From the results of erythrocyte URO-D activity, the frequency of type II PCT is estimated at 25.0% of PCT cases, a percentage similar to that found in other countries.[23] Two cases were classified as type III PCT in 124 unrelated patients, but we cannot discard the possibility that some patients classified as type I were in fact type III, as an exhaustive knowledge of family history was not available in all of these patients.

In other populations studied, PCT was more frequent in men than in women, but the sex ratio varies widely from country to country.[23] In Argentina the men to women ratio is 4:1, however, when we considered the two types of PCT separately, this ratio was about 5:1 for type I PCT and 1:1 for type II PCT, indicating that genetic deficiency in the URO-D is a predisposing factor in the clinical development of PCT, and that such deficiency makes men and women equal as regards to the involvement of triggering factors. Interestingly, for infantile-PCT cases this ratio was also about 1:1, and in all of those patients in whom erythrocyte URO-D activity was measured, they were found to be type II PCT cases. It is possible that in infantile-PCT cases, a genetic URO-D deficiency is related with the early onset of the disease. The different sex ratio in adults could be

related to greater exposure to precipitating factors in men than in women.

In our population, alcohol is the most frequent precipitating factor, but in women, oral contraceptives and postmenopausal estrogen replacement therapy are the most important risk factors for PCT development, as reported for other populations.[20,33] Exposure to polyhalogenated compounds, such as hexachlorobenzene, is rarely reported in the present, but in this retrospective study, it was observed in a high number of patients (13.0%), all of whom were from rural areas and/or worked in agriculture or in the production of pesticides.

In approximately 30% of our patients the precipitating agent or agents could not be identified from their clinical histories (Table III), but complete data from patients are not available in all cases. Moreover, other factors such as deficiencies of antioxidants, were not investigated in these patients. Therefore, the number of patients in whom at least one known factor is present would be underestimated.

It is well known that alcohol is an important precipitating factor that may cause disturbances in porphyrin metabolism in healthy individuals, as well as biochemical and clinical manifestations in acute and chronic hepatic porphyrias. Alcohol promotes the enzymatic failure of the decarboxylation of uro- and heptaporphyrinogen, and this is followed by a hepatic accumulation of uro- and heptaporphyrin and their urinary excretion.[34] Alcohol induces P450 enzymes and promotes the generation of reactive oxygen species, thus contributing to oxidative stress.[35] Moreover, alcohol induces ALA synthase and enhances iron absorption.[35] Thus, alcohol would act as a risk factor for PCT development mainly because of its action as a porphyrinogenic agent and its effect on iron metabolism, and it could also have a synergic effect with other factors, such as HFE gene mutations.

Hereditary hemochromatosis is currently considered as the main factor in explaining iron overload. Several studies on the analysis of the frequencies of HFE mutations in each type of PCT indicate that the presence of C282Y and H63D mutations in homozygosis or heterozygosis is an important susceptibility factor for the development of both types of PCT.[21,33,36-39]

Our findings, in a study of 30 unrelated Argentinean PCT patients, indicated that H63D is the most frequent HFE mutation, as has been reported for Italian[22] and Spanish people,[33,36] and this is in keeping with the fact that most of the Argentinean population has Italian or Iberian ancestry. No patient had the S65C mutation, which is associated with a mild form of hemochromatosis,[40] and just one patient had the C282Y mutation. Although the number of patients studied was small and the lack of any data about the frequency of HFE gene mutations in Argentina does not allow a statistical comparison, our results on the prevalence of HFE gene mutations in PCT patients showed a higher frequency in type I PCT (70%) than in type II PCT (45%). These frequencies were also higher than in control populations from Spain and Italy,[22,36] the main ancestral countries of the Argentinean population.

Reports, mainly based on retrospective studies, have shown a high prevalence (76%-95%) of HCV infection in PCT patients from Southern Europe[9,41-44] and the United States (50%-75%).[45,46] In contrast, a low prevalence (6%-18%) has been found in Holland, Ireland, Germany, New Zealand, and South Africa.[47-51] In our country, the prevalence of HCV infection in PCT patients is 35.2%, while in the general Argentinean population, it is 1.0%.[52] Moreover, we have gone a little further and shown that 1b genotype was the most prevalent among PCT-HCV Argentinean patients (72.2%).[53]

In all our anti-HCV positive patients, HCV RNA was detected by RT-PCR, indicating an active replication of the virus. It is possible that in these patients HCV infection and subsequent liver injury is implicated in the clinical expression of PCT. Alcohol intake was present in 63.2% of these patients, but the higher prevalence of HCV in PCT patients than in the general Argentinean population suggests a causal association. Although the connection between HCV infection and PCT is now well documented, the nature of the association is not yet clear. Moran et al[54] have proposed that HCV does not have a direct effect on hepatic URO-D activity, and that it is more likely that the C virus induces the expression of a latent defect in URO-D in asymptomatic patients. These authors considered that, during the process leading to PCT in HCV infection, there may be involvement of other genes whose expression induces hepatic URO-D inactivation.[54]

Data obtained from Argentinean PCT-HIV patients indicated that in about 90%, alcohol abuse and/or infection with hepatitis viruses were potential precipitating factors. As a consequence of an early exposure to these factors, earlier onset of the porphyria in PCT-HIV patients than in the general PCT population was observed. We suggest that the high incidence of PCT associated with HIV infection might be caused by exposure to factors such as alcohol and hepatotropic viruses, and not to a direct role of HIV infection on porphyrin metabolism.

In this retrospective study we have found that a number of both inherited and environmental

factors are associated with the phenotypical expression of PCT in susceptible individuals, and that in some cases more than one factor may contribute to the development of the porphyria, indicating that PCT is a multifactorial disease.

Moreover it is clear from our findings that, for improved management of the disorder, it is of great importance to identify all specific risk or etiological factors that contribute to the development of PCT, although the mechanisms underlying the hepatic URO-D deficiency leading to the disease yet remain unknown.

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