Porphyria cutanea tarda and liver disease
A retrospective analysis of 17 cases from a single centre and review of the literature

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Abstract

Background/aims : **Sporadic Porphyria Cutanea Tarda (sPCT) is associated with liver disease, e.g. HCV infection, haemochromatosis and especially alcoholic liver disease. We conducted a retrospective analysis on the prevalence of liver disorders in association with Porphyria Cutanea Tarda (PCT), in a university referral centre.**

Methods : **The PCT cases were retrieved from computerized databases. Patient files lacking information on the presence of concomitant liver disease were excluded from further analysis.**

Results : **29 PCT patients were retrieved from our databases, of which 17 patients with sPCT were retained for further analysis. Patients were middle aged (mean age : 43 ± 3) and there was no gender difference (10 males vs. 7 females). Almost all patients had iron overload (14/17). 5 patients had chronic HCV, with type 1b in 3 of them, 7 abused alcohol, 4 patients had hereditary haemochromatosis (3 homozygous C282Y – 1 heterozygous H63D/C282Y). In 3 patients sPCT was associated with medication intake and one patient had chronic hepatitis B (HBV). 13 patients were treated with phlebotomies, with success in 11/13. 4 patients were treated with chloroquine, 3 of which also underwent phlebotomies. Of the 5 patients with HCV, 3 were successfully treated with combined antiviral therapy ; one of them is planned to be treated ; one patient never received therapy and was lost from follow-up. One patient developed hepatocellular carcinoma (HCC) during a median follow-up of 24 years.**

Conclusions : **We found a significant association between sPCT and liver disorders, such as chronic HCV infection, alcohol abuse, iron overload and hereditary haemochromatosis. Therefore, patients presenting with PCT should be screened for concomitant liver disease. Iron overload is present in a majority of patients, the majority of patients can be successfully treated with phlebotomies. The risk of developing HCC in our sPCT patients and in literature is low.** (Acta gastroenterol. belg., **2008**, 71, **237-242**).

Introduction

Porphyrias are a heterogeneous group of metabolic diseases caused by a defect or dysfunction of enzymes of the haem biosynthesis pathway, leading to accumulation of different porphyrins and other toxic haem precursors in cells. Haem is synthesised in every human cell, but about 85% is made in the erythroid cells, where the majority is used for haemoglobin formation. Most of the remainder is produced in the liver, where 80% is used for the creation of different cytochromes. Seven different genetic porphyrias are identified, each resulting from mutation of the gene for a specific enzyme of the haem biosynthesis pathway, but also acquired forms are described.

Porphyria Cutanea Tarda, PCT, is the most common form of porphyria. PCT is caused by deficiency of the enzyme Uroporphyrinogen Decarboxylase (UROD) and classified in three types : Type I, a non-inherited sporadic PCT occurs in 75% of patients. It usually presents in middle age and is caused by an enzyme deficiency restricted to the hepatocytes. Type II, familial PCT, occurs in the majority of the remaining 25%. This form usually develops by the age of 20, is inherited in an autosomal dominant pattern and caused by an enzyme deficiency in all tissues. Type III disease is a rare inherited form in which the enzyme deficiency is only located in the liver (1,2).

Since the enzyme defect in sporadic PCT (type I : sPCT) is restricted to the hepatocytes, uroporphyrins accumulate in the liver and cause liver dysfunction. Typical needle-like lesions, the crystal porphyrins, are seen in the mitochondria. Via blood, porphyrins also accumulate in skin, urine and faeces. They are phototoxic to the skin and give the characteristic symptoms of chronic blistering on sun-exposed areas. Diagnosis of sPCT is made by analysis of excreted uroporphyrins in the urine. Sporadic, acquired PCT has an estimated incidence of 2-5 per million per year and a prevalence of 1/10 000 (3).

Besides deficiency of UROD enzyme, additional factors are necessary to make the disease clinically manifest. The current theory is that sPCT develops in patients with liver diseases, specifically chronic hepatitis C virus (HCV) infection, hereditary haemochromatosis (HH) and alcoholic liver disease.

To further study this hypothesis, we conducted a hospital-based retrospective analysis to examine all our recorded cases of sPCT for the presence or absence of liver disease and its correlation with sPCT. We describe

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Table 1. — Clinical, biochemical and pathological characteristics of our patient cohort

N°	ABNORMAL LIVER TESTS	INCREASED IRON	LIVER BIOPSY	TRIGGER FACTOR	TREATMENT	OUTCOME
1	+	+		**ETHYL**	Phlebo chloroquine	Relapse
2	+	+	Crystals - fibrosis - siderosis	**HCV (1a)**	Phlebo	R
3	+	+		**barbiturates**	Phlebo	R
4	+	+	fibrosis	**ETHYL** **HH C282Y(+/+)**	Phlebo	R
5	+	+		**HCV (1b)**	Phlebo IFN-ribavirin	R
6	+	+	Siderosis - fibrosis	**HH C282Y** **HBV**	Phlebo	R
7	+	+	crystals - siderosis steatosis - fibrosis	**ETHYL**	Phlebo	R
8	+	+		**Orthonovum** **ETHYL**	Phlebo chloroquine	R
9	+	+		**HCV (1b)** **HCC - Tx**	Phlebo	
10	+	+	crystals	**ETHYL**	Phlebo chloroquine	R
11	+	+		**ETHYL** **HCV(?)**	Phlebo	
12	+	+		**HH C282Y (+/+)**	Phlebo	R
13		+		**?**		
14	+	+		**HH H63D/C282Y**	phlebo	R
15				**Estrogen**	Stop estrogen	
16	+	+	Fibrosis - cirrhosis	**HCV (1b)** **ETHYL**	IFN - ribavirin	R
17	+	+		**HCV (1b)** **ETHYL**	Nivaquin	R

17 patients with sPCT were retained from our databases and were further analyzed. Rows : patients.

Columns : presence or absence of disturbed liver tests ; presence or absence of biochemical iron storage ; liver biopsy result ; trigger factor ; treatment ; outcome.

Abbreviations used : HCV : hepatitis C virus ; HBV : hepatitis B virus ; HCC : hepatocellular carcinoma ; Phlebo : phlebotomies ; LTx : liver transplantation ; R : regression of skin lesions and normalisation of liver tests.

a case series of 17 sporadic PCT patients and review the pathophysiology of sPCT in liver disease.

Methods

Using the available computerized databases in our hospital, we carried out a retrospective analysis of all cases of sPCT, diagnosed from 1978 on. The inpatient and outpatient files were searched for indices of liver disease in association with PCT. We looked in to the biochemical and histological data, their treatment and outcome. Part of our patients was lost from follow-up. Family doctors were contacted for further information about their evolution. Patient files lacking information on absence or presence of concomitant liver disease and inherited forms of PCT were excluded from further analysis. Diagnosis of PCT was based on urine uroporphyrin ratio and in some patients also on skin biopsy.

The aim of our study was to characterize our population of sPCT patients and to investigate this population for the prevalence of associated liver disorders and documented treatment and outcome.

Results

We documented 29 patients with PCT and retained 17 patients with sporadic PCT and concomitant liver disorder, in a period of 28 years (Table 1). Patients were middle aged (mean age : 43 ± 3) and no gender difference (10 males vs. 7 females) was found. All but one patient were west-European Caucasian in origin ; one patient was from north-African descent. Almost all patients had biochemical indices of increased iron stores and liver siderosis was documented in three of them on liver biopsy. In our population, alcohol, HCV and hereditary haemochromatosis were the most commonly associated factors. 29% were triggered by several factors (Fig. 1). Five patients (35%) had chronic HCV infection, with type 1b in three of them. Seven patients (47%) abused alcohol, four patients (24%) had hereditary

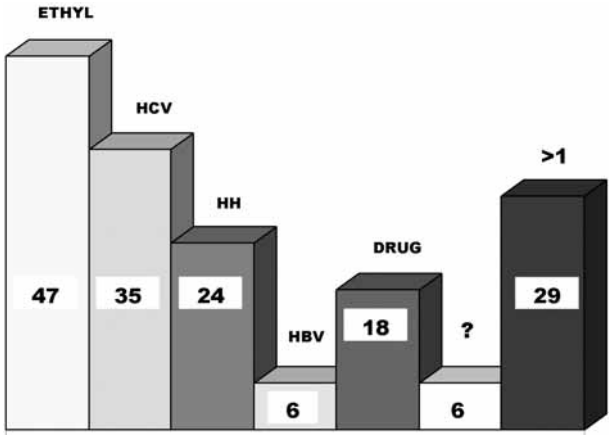

Fig. 1. — Liver disorders associated to sPCT.
Type and frequency of liver disorders associated with sPCT in our cohort of patients are represented in the graph. Abbreviations used : Ethyl : alcohol abuses ; HCV : chronic hepatitis C virus infection ; HH : hereditary haemochromatosis ; HBV : chronic hepatitis B virus infection ; DRUG : medication intake ; Unknown : no specific associated factor found ; > 1 : more than one of the above factors were found associated to sPCT occurrence.

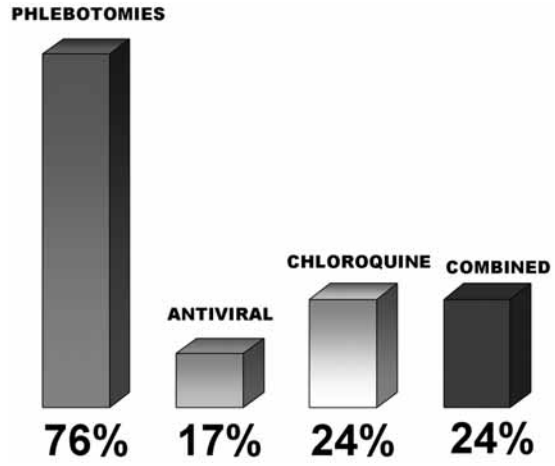

Fig. 2. — Installed treatment for sPCT in our patient cohort.
Abbreviations used :
Antiviral therapy (combination of Ribavirin and Interferon) ; Combined therapy : i.e. antiviral therapy and phlebotomies.

haemochromatosis, three were homozygous C282Y, one patient had a combined heterogeneous genotype H63D/C282Y. In three patients (18%) sPCT was associated with medication intake and one patient had chronic HBV infection.

The majority of our patients (13 patients : 76%) were treated with phlebotomies, with clinical response in 11 (80% had regression of skin lesions). Four patients (24%) were treated with chloroquine and 3 of them also received phlebotomies Of the 5 patients with HCV, 3 (12%) were successfully treated with combined antiviral therapy ; one of them is planned to be treated and one patient never received therapy and disappeared from further follow up (Fig. 2). Most of the patients treated had a- normalisation of liver test and function, and a regression of skin lesions, except one. This patient developed HCC in a cirrhotic liver during a median follow-up of 24 years.

Discussion

The overall incidence and prevalence of sPCT is estimated at 2-5 million patients per year and 1/25 000 in Western-European countries.

The pathogenesis of PCT is still poorly understood. In all forms of PCT, hepatic UROD activity appears to be decreased despite a normal concentration. In contrast to familial forms of PCT, the UROD gene is not mutated in sporadic PCT. This implies an inhibition of the enzyme although the responsible inhibitors remain unknown. Several studies have already discussed the role of iron, however.

Iron probably plays a central role in the development of PCT (4). This has been known for decades. Almost all PCT patients have increased stainable iron in the liver. The majority have liver siderosis, increased body iron stores, and biochemical evidence of iron overload. Correction of iron overload by venesection restores normal enzyme activity and reduces clinical symptoms. In contrast, iron supplementation provokes relapse of the disease (2).

Iron may inhibit UROD in two ways, by a direct interaction with the essential sulphydryl groups of the enzyme or indirectly, due to generation of free radicals, which might interact directly with the enzyme and/or oxidize the porphyrinogen substrates to non-metabolisable accumulating porphyrins (2,5).

The cause of iron overload in the liver is not known. A disturbed iron metabolism has been observed : it may be secondary to different exogenous trigger factors or genetically determined. Approximately 40% of PCT patients are either homozygous or heterozygous for the C282Y mutation (35-38). On the other hand, Italian PCT patients do not have an increased prevalence of the C282Y mutation, they have a higher prevalence of the H63D mutation (39). Japanese patients with PCT show no correlation with C282Y mutation (41), and in Spanish patients the compound H63D/C282Y subjects seem at higher risk for sporadic PCT (54).

In our study, we could confirm biochemical iron overload in 14/17 cases. Increased iron staining in liver tissue was demonstrated in 4. In 4/17 cases, the iron overload was associated with mutations in the HFE gene (3 homozygous for the C282Y mutation, one compound heterozygous (H63D/C282Y)). Treatment with phlebotomies was successful in 14/17. The frequency or volume of phlebotomies to reach normal or low biochemical iron load was not different between the group of patients with

homozygous of compound heterozygous HFE mutations and the group without these genetic variants (i.e. on average 400 cc every 2 months in both groups).

The inhibition of the UROD enzyme by iron does not seem to be sufficient to cause the disease. Additional trigger factors are thought to be necessary to make the disease become clinically manifest. These factors include alcohol, hepatitis C virus, estrogens, cytochrome polymorphisms, changes in the transferrin receptor 1 gene and HIV infection. In 80 % of the patients, one or more factors are present (6,7).

In our study alcohol and HCV were most frequently associated factors. Therefore, they are discussed in more depth here.

PCT and alcohol

Already years ago, it was described that alcohol is a major risk factor for PCT and the factor commonly associated with its development. Alcohol abuse has been identified in 30-90% of patients with PCT (8,9). On the other hand, sPCT is an uncommon complication of alcoholism. In a Scandinavian study only 2% of alcoholics with cirrhosis had signs of PCT (10). Evidence for a dose-response relationship between alcohol and PCT has yet not been shown by studies. Alcohol is an important factor in the pathogenesis of PCT but is not a predictable cause of the disease.

Ethanol is a drug metabolised by hepatic microsomes (11). Such drugs stimulate their own metabolism, in which haem synthesis is involved, and affect porphyrin synthesis in various ways. Since 1935, when Franke and Fikentscher reported that ethanol consumption increases urinary porphyrin excretion, the association of haem biosynthesis with ethanol ingestion has been studied by several groups like Brugsch (1937), Sutherland and Watson, 1951 ; Orten *et al.*, 1963 ; Elder, 1976 ; McEwin, 1976 ; Doss, 1980 ; McColl *et al.*, 1980 ; Sieg *et al.*, 1991 ; Schoenfeld *et al.*, 1996) (11).

There are several possible mechanisms of the role of alcohol in PCT. Alcohol increases iron absorption resulting in iron accumulation in the liver and systemically. By inducing -aminolevulinic acid synthase (hepatic ALA synthase), alcohol could have an inhibiting effect on UROD (6,9,11). Alcohol could have an indirect effect on UROD by stimulating the production of free radicals, which result in oxidative damage in hepatocytes in the presence of iron. And finally, recent studies show that hepatotoxins such as alcohol may release stored iron from ferritin in a form that catalyses the formation of reactive oxygen species and thus switch on the inactivation (11). Abstinence from alcohol is a therapeutically and important preventive measure in all types of symptomatic hepatic porphyrias (6).

Also in our study we see a clear association between alcohol use and sPCT. It was present as a potential precipitating and aggravating factor in 7/17 (47%) cases of sPCT.

PCT and HCV

The association between PCT and HCV has been showed by several articles and studies. *Gisbert and colleagues* (12) presented a systematic review and meta-analysis of fifty studies including 2,167 patients with PCT, on the prevalence of associated HCV infection. Mean HCV prevalence by serology was 47%, and 50% with polymerase chain reaction (PCR). They noted a marked variation depending on the country and the type of PCT (57% in the sporadic and 26% in the familial form).

This geographical variation suggests underlying environmental and/or genetic factors. Sun exposure, alcohol use and the geographical variation in HCV itself (marked increase in Southern Europe), could be responsible environmental factors. As for genetic factors, the geographical variation of the HFE gene, TNF-receptor, Transferrin receptor-1 and URO-D may also be important (13). However, one has to be cautious about reported HCV infection rates. Serological testing may overestimate active HCV infection detected by PCR. In the meta-analysis of Gisbert *et al.*. the association with HCV was not significant when they included studies evaluating HCV infection by PCR only.

In contrast to the analysis of Gisbert *et al.*. recent studies report a prevalence of only 5% or less for the association of PCT and HCV infection (13,14,15). Secondly, some studies have reported a specific genotype of HCV (type Ib) to be present in nearly 90% of PCT patients (16), others did not find a genotypic correlation (17-21). HCV infection may be not only a precipitating factor of PCT, but also an aggravating factor since in HCV-infected patients biochemical and histological parameters were worse than in non-infected patients. Interferon therapy, as a standard treatment for HCV, showed a favourable response in PCT symptoms (22-24). Several authors did not confirm these findings (25-28). De novo occurrences of PCT during interferon therapy in association with ribavirin have even been described by Jessner *et al.* (29) and Thevenot *et al.* (30). It has to be noted that haemolysis is a well-known side effect of ribavirin and in this way may increase hepatic iron storage and stimulate haem production. Although the response of PCT disease to interferon therapy is positive, the response of HCV infection and viral load is poor compared to subjects without PCT. This suggests the resolution of PCT may not be related to the virus per se (31).

Recently PCT as an extrahepatic manifestation of HCV infection has been pointed out by El-Saref and colleagues (33). This is important because it implies patients with PCT should be tested for HCV infection and signs and symptoms of PCT should be sought in patients with chronic HCV (34).

Also in our analysis we see an association of HCV with sPCT. The association is not common. HCV infection is estimated to have a prevalence of 1% in the

Belgian population (40). Of the 647 patients with HCV in follow up in our centre, we found 5 patients with sPCT (0.8%). There was a similar prevalence of genotype 1b virus in our sPCT cohort as in our general HCV-infected population (HCV patients : n = 647, type 1b : 226/647 ; PCT patients : n = 5, type 1b : 3/5). Our patients were treated with interferon alpha and ribavirin together with phlebotomies ; 4/5 showed sustained viral response and 4/5 resolution of the skin signs.

The frequency of HCV infection in our cohort of PCT patients (35%) is compatible with the reported 50% prevalence (12).

PCT and HCC

Several reports have suggested that patients with PCT are at high risk of developing HCC (44-47). This was, however, not confirmed in other studies (48-50).

For example, one study evaluated the incidence of HCC in 39 patients with PCT and assessed the possible co-factors. HCC was diagnosed in 1/39 patients with PCT (cumulative incidence, 2.6%), giving a yearly incidence of 0.26% per patient-year (51). This study shows that the risk of developing HCC in patients with PCT in that area (Spain) is relatively low and perhaps attributable to concomitant co-factors, such as HCV infection.

Some authors even reported that HCC in PCT patients occurs only in case of cirrhosis (51). Knowing that PCT is associated with potential carcinogenic factors such as hepatitis viruses, alcohol, and iron overload, the development of HCC may represent the final step of the effects of these various precipitating agents. Iron overload in the liver may promote hepatic carcinogenesis via DNA damage and lipid peroxidation caused by oxyradicals (52).

Also in our study the incidence of development of HCC in PCT patients is very low (1/17 in 24 patient years).

We conclude that the association of PCT and HCC exists, but in our series can not convincingly be correlated with PCT, because in the single patient that developed HCC, other potentially carcinogenic factors (chronic HCV infection) were present. Patients presenting with PCT should undergo both HCV infection determination and liver biopsy, and those with concomitant HCV infection or advanced fibrosis/cirrhosis should be included in a standard surveillance programme in order to achieve early diagnosis of HCC.

In conclusion, the present retrospective analysis confirms that iron overload is seen in a large majority of sPCT cases and that there is an association with alcohol, hepatitis C and haemochromatosis, alcohol being the most commonly associated factor. Treatment with phlebotomies was successful in the majority of patients. Only one case of HCC was documented until now, and probably the concurrent presence of multiple potential carcinogenic factors is responsible for this development.

Based on our retrospective study and compared to other studies, sPCT seems underdiagnosed. This may be related to uncommon referral by dermatologists, but in view of the commonly associated liver disease, we plead for a multidisciplinary approach.

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