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CLINICAL REPORT

# The Prevalence of Hepatitis C in Patients with Porphyria Cutanea Tarda in Stockholm, Sweden

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**In many countries hepatitis C virus infection has been considered a major factor triggering overt porphyria cutanea tarda. The prevalence of hepatitis C virus infection was retrospectively studied in 87 patients who during a period of 11 years were diagnosed with porphyria cutanea tarda in Stockholm. Among patients with the sporadic form of porphyria cutanea tarda, the prevalence of hepatitis C virus infection was 36.4%. As hepatitis C virus infection may today be successfully treated and as the infection may be clinically silent and thus unknown to the patient, it is important to screen all patients with porphyria cutanea tarda for hepatitis C virus infection.**
***Key words: porphyria cutanea tarda; sporadic; familial; hepatitis C infection; prevalence.***

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Porphyria cutanea tarda (PCT) is the most common of the porphyrias worldwide (1). The main symptoms are increased skin fragility leading to blisters and scars on the upper side of the hands. Hyperpigmentation and hypertrichosis can be seen on the face. Only areas exposed to the sun are affected. The metabolic basis of the disorder is an accumulation of phototoxic porphyrins in the skin secondary to deficient activity of the hepatic enzyme uroporphyrinogen decarboxylase (UROD), the fifth enzyme in the haem biosynthetic chain. The catalytic activity of UROD must decrease by at least 75% before polycarboxylated porphyrins, primarily uroporphyrinogen and heptacarboxylated porphyrinogen, accumulate to levels causing the characteristic biochemical and clinical photosensitization. There are two main forms of PCT, a sporadic form (S-PCT) with no known genetic background and a familial form (F-PCT) in which the enzyme activity is decreased due to mutations in the UROD locus (2). The onset of overt PCT is aggravated by many factors, all associated with hepatosiderosis (3). In addition, hepatitis C virus infection (HCV) has been implicated as a major precipitating factor (4–7), although with very varying prevalence throughout Europe (4–11).

The aim of the present study was to survey the prevalence of HCV in patients who had been diagnosed with PCT during a period of 11 years in Stockholm.

## PATIENTS AND METHODS

In the Stockholm region, all analyses for porphyria are performed at the Porphyria Centre Sweden at Karolinska University Hospital Huddinge. We gathered all patients who between 1990 and 2000 (11 years) were diagnosed with PCT. The biochemical diagnosis of PCT was based on increased urinary excretion of polycarboxylated porphyrins (urine porphyrin $>25$ μmol/mol creatinine and $>60\%$ were polycarboxylated porphyrins), a strong fluorescence peak at 620 nm in the plasma and isocoproporphyrin in the stools (2).

Erythrocyte UROD [EC 4.1.1.37] was measured by established methods (12, 13) using 5-COOH-porphyrinogen I as a substrate. Results are expressed as a percentage of normal activity. Patients with low erythrocyte UROD activity ($<68\%$) were classified as hereditary or F-PCT, and those presenting a normal activity of UROD ($\geqslant 68\%$) were classified as S-PCT.

Altogether, 87 patients (51 men aged 32–81 years and 36 women aged 23–85 years) had been diagnosed as having PCT during the study period. Most of the patients had been diagnosed at one of the four departments of dermatology in Stockholm, only a few by dermatologists in private practice or in departments of internal medicine. Clinical data concerning HCV testing were gathered from all these colleagues. In 53 (61%) of the cases, anti-HCV screening had been performed at the time of the biochemical PCT diagnosis. Seventeen samples were investigated retrospectively using a blood sample stored since the time of the PCT diagnosis. Of the remaining 17 patients, 8 were dead and 5 could not be found. The remaining four patients were requested to attend for anti-HCV investigation at one of the two dermatological clinics and two persons accepted. Thus a total of 72 patients (42 men and 30 women) were tested for HCV. Forty-four of these patients were classified as S-PCT and 23 as F-PCT. In five, no differential diagnosis between these two forms was performed as no blood was available for UROD analysis.

The HCV analysis performed retroactively, using a stored blood sample, was made by analysis of HCV-antibodies (Ortho® HCV 3.0 ELISA Test System with Enhanced SAVe, Ortho Diagnostic Systems, Raritan, NJ, USA). The detection of serum anti-HCV antibodies in patients tested at the time of PCT diagnoses was made by ELISA tests with different kits. The remaining patients were requested to attend for anti-HCV investigation at one of the two dermatological clinics participating in the study. For these patients, the HCV analyses were performed by a micro-ELISA test, confirmed with anti-HCV RIBA-test.



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The study was approved by the local ethics committee of the Karolinska Institute (Dnr 216/00), Stockholm, Sweden.

## RESULTS

Of the 72 patients tested for HCV, 19 patients (26.3%) – 16 men (aged 45–67 years) and 3 women (aged 49, 52, 66 years) – were anti-HCV-positive (Table I). Of these, two were discovered to be anti-HCV-positive when recalled in connection with the present investigation and one among the stored blood samples from the time of biochemical PCT diagnosis. Thus the positive anti-HCV test in most of the patients was discovered before or at the same time as the PCT diagnosis was settled.

## DISCUSSION

HCV is found all over the world with a prevalence of about 3% (14), but there are great differences between countries. In Egypt and some parts of Italy, the frequency is as high as 30% (14). In Sweden the prevalence of HCV varies between 0.1 and 0.5% (15).

During the past decade many reports have shown the association of HCV infection and PCT. The prevalence of PCT patients affected by HCV infection varies in different countries. The highest frequencies, ranging between 60 and 80%, have been reported from Italy, Spain and France (4–7). Much lower frequencies have been reported from Germany, Ireland and Denmark (8%, 10% and 3%, respectively) (9–11).

Our study is the first report from Sweden showing the prevalence of HCV among patients with PCT. Extensive efforts were made to find all patients with the diagnosis of PCT in Stockholm over a period of 11 years. This was facilitated by the fact that all the biochemical porphyria investigations were done at the Porphyria Centre Sweden. The diagnostic registers of the dermatological clinics confirmed that all patients with PCT were included on the Centre's list. Therefore we may conclude that almost all the patients diagnosed as having PCT during these years were included in our study. All the patients had clinical symptoms of PCT at the time of diagnosis. In approximately 60% of the patients an anti-HCV screening test was done at the time of PCT diagnosis. We are aware of the fact that a positive anti-HCV antibody test is not always equivalent to an active infection, as many patients may be healed completely. However, as the patients were investigated and treated in different clinical specialities, it was not possible to evaluate the clinical impact of the anti-HCV antibody screening test. All the anti-HCV-positive patients had been referred to, or had already been examined in, a department for infectious diseases. In the present retrospective study it was not possible to follow-up the stage of HCV infection or different modalities of treatments performed by the respective infectious ward. In three patients the positive anti-HCV antibodies were discovered during this study. In one of these, the diagnosis was made using a blood test stored at the time of PCT diagnosis; the other two, diagnosed on recall, had no medical histories of blood transfusion or intravenous addiction after the diagnosis of PCT. We therefore assume that the HCV infection occurred prior to the debut of PCT. Only one of the 23 patients with F-PCT had HCV infection (Table I).

Table I. *The prevalence of hepatitis C virus (HCV)-antibodies at the time of diagnosis in 72 patients with porphyria cutanea tarda (PCT) in Stockholm during the years 1990–2000*

| | S-PCT | F-PCT | U-PCT | Total |
|---|---|---|---|---|
| No. of patients | 44 | 23 | 5 | 72 |
| HCV positive, *n* | 16 (36%) | 1 (4%) | 2 (40%) | 19 (26%) |
| Men | 14 | 1 | 1 | 16 |
| Women | 2 | 0 | 1 | 3 |

S-PCT, sporadic PCT; F-PCT, familial PCT; U-PCT, unclassified PCT (i.e. not further investigated by enzyme analysis).

The prevalence of HCV infection in patients with S-PCT was 36.4%. Thus, the prevalence of HCV infection in Swedish patients with S-PCT is much higher than previously reported from northern Europe (9–11). A reason for this finding could be that Stockholm, like other big cities, has a relatively high frequency of intravenous drug addicts. Sixteen of the 19 HCV-infected patients were men, a frequency that is in accordance with findings in other studies (5, 16).

Overt PCT is associated with strongly decreased UROD activity in the liver. The onset of symptoms usually occurs during the fourth or fifth decade of life. S-PCT is the most common form of PCT and there is no genetic defect at the UROD locus. F-PCT is less common and is inherited in an autosomal dominant way with incomplete penetrance. In our study, all but one of the patients found to be anti-HCV-positive had S-PCT. In previous reports the association has also been seen principally for S-PCT (6, 8). A Danish report found only one patient among 30 investigated PCT patients with positive HCV serology (i.e. 3%); the patient belonged to the F-PCT subgroup (11).

Many of the patients with PCT were investigated for HCV at the time of PCT diagnosis (or blood was sampled at that time), indicating that HCV infection preceded the onset of PCT symptoms in the affected individuals. In many patients, however, it was not possible in this retrospective study to date the anti-HCV test.

HCV has been implicated in many countries as the major precipitating factor in overt PCT (4–6). However, O'Reilly et al. (17) found no abnormalities in porphyrin metabolism in two different groups of patients with hepatitis C infection. One group consisted of women who had been contaminated almost 20 years earlier by infusion of anti-D immunoglobulin during delivery. The

other group consisted of both men and women who were HCV-positive secondary to intravenous drug abuse. From the O'Reilly study (17) it may be concluded that HCV infection alone is insufficient to cause porphyrin metabolic derangement. Thus, in predisposed individuals multiple insults to the hepatocyte appear to be necessary to exert the profound inhibition of UROD activity that is described in overt disease (2, 3). Removal of iron by repeated phlebotomies always leads to clinical and biochemical remission, even in patients without increased liver or total body iron (18). Although the role of iron in the pathogenesis of PCT is not entirely clear, it seems likely that iron facilitates the formation of products capable of inhibiting UROD. Several noxious factors such as increased iron stores, alcohol abuse, oestrogen therapy, hepatotoxic medication or viral hepatitis have been shown to trigger the clinical onset of PCT (2, 3).

The mechanism of the triggering effect by viral hepatitis remains largely speculative. It has been suggested that HCV decompartmentalizes iron to create 'free iron', a process that may lead to the formation of active radicals and oxidation of uroporphyrinogens to UROD inhibitors (4–6). The importance of iron has been stressed by several reports showing a high prevalence of haemochromatosis mutation in patients with PCT (19), and the same pattern has been found in Sweden (20).

The available data suggest that HCV infection is an important aetiologic factor in PCT. Cirrhosis, hepatic failure and primary hepatocellular carcinoma are all possible complications of HCV infection, although the infection may often remain clinically silent and therefore unknown to the patient for several years. Today, treatment with a combination of interferon and ribavirin often cures the infection and improves the liver histology and function, as well as the outcome of PCT treatment. Therefore, awareness of the relatively high co-morbidity of these two diseases prompts investigation of every patient with PCT for HCV infection. Moreover, as patients with PCT are often phlebotomized, it is important for medical staff to be aware of a possible HCV infection when handling the blood.

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