Porphyria Cutanea Tarda

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Porphyria cutanea tarda (PCT), or chronic hepatic porphyria, is the most common type of porphyria, with characteristic skin and laboratory abnormalities. PCT results from a decreased activity of the enzyme uroporphyrinogen decarboxylase (URO-D) in the liver (1, 2).

PCT is not a single monogenic disorder and is now classified in three different forms, the commonest sporadic type (Type I) having no family history and a normal erythrocyte URO-D activity, with the enzyme deficiency restricted to the liver. Type I is frequently associated with exposure to various porphyrinogenic agents such as alcohol, oestrogen and iron.

In Type II or the familial type of PCT, URO-D activity is reduced to about 50%, both in erythrocytes and the liver as well as in other tissues, caused by an inherited, autosomal dominant defect. Type II is seen at a younger age than the other types, and a very early onset suggests its presence.

A third, very rare, Type III form has recently been described with a familial occurrence and the enzyme defect confined to hepatocytes, like in the sporadic type, but not in erythrocytes. Thus, PCT does not have a simple pattern of inheritance, and the three known forms are clinically indistinguishable in the absence of a family history.

In addition, toxic forms of PCT have been known to occur after exposure to various chemicals that may inhibit hepatic URO-D activity. For example, a well-known outbreak occurred in Turkey in the late 1950s following the consumption of grain contaminated with the hexachlorobenzene fungicide (3). Another example was caused by an industrial accident in which a dioxin (TCDD) was released (4).

Provocative factors

Various common agents, like iron supplementation, alcohol and steroid hormones (estrogens), which under normal circumstances do not cause porphyria, are known to provoke PCT in susceptible individuals (5, 6), but a liver lesion seems to be a prerequisite for induction of the full clinical and biochemical syndrome.

It is well known that hepatic siderosis and high serum iron levels occur in most PCT patients. The role of genetic hemochromatosis in the pathogenesis of iron overload in PCT has been hypothesized for many years but it is only recently that the genetic defect causing hemochromatosis has been identified. There are two known mutations in the hemochromatosis gene (HFE): cystein 282 tyrosine (Cys282Tyr) and histidine 63 asparagine (His63Asp) (7, 8, 9). A recent Swedish study including both familial and sporadic PCT patients showed that 60% of the patients were carriers of one or two mutations in the gene for hemochromatosis (P. Harper, personal communication). Iron overload is one of the factors that trigger off the clinical manifestations of PCT, and iron depletion remains an important factor in the therapy (10, 11). Iron inhibits catalytic activity of URO-D without decreasing the concentration of enzyme protein, and this inhibition is reversible (12, 13).

Hepatotropic viruses causing chronic hepatitis, particularly hepatitis C virus, have also been implicated in the pathogenesis of PCT (14-17). Other hepatic disorders, liver cirrhosis and primary hepatomas sometimes appear in the case history of a patient with PCT, and should be excluded before diagnosis.

The association between PCT and HIV infection has also been recognized (18) and known to precipitate PCT (19, 20). In a recent study, 50% of HIV-positive patients had abnormal porphyrin metabolism. Furthermore 89% of them were also anti-HCV positive (21).

Investigations indicate that multiple insults to the hepatocyte appear necessary, as for example HIV and/or HCV infection, in association with further damage caused by either iron overload, alcohol abuse, or oestrogen therapy (22).

Associated conditions

Some liver cell damage is seen in most PCT patients, as revealed by needle biopsy. The most frequent findings

are mild fatty infiltration, focal necrosis and inflammation of fibrotic portal tracts (23). Cirrhosis is present in less than 15% of the cases but has been considered a greater risk for the development of hepatocellular carcinoma than in other types of cirrhosis, especially in men over 50 years of age (24).

Whether the porphyrin accumulation is more important for the initiation of the hepatocyte damage or for its progression is not fully known. PCT has also been described in connection with a wide range of other conditions, particularly non-insulin-dependent diabetes mellitus (1, 2).

Differential diagnoses

The most important differential diagnoses to PCT are the acute porphyria forms with cutaneous findings, e.g. variegate porphyria and hereditary coproporphyria (1, 2), but also drug-induced pseudoporphyria and the bullous dermatoses of chronic renal failure.

Pseudoporhyria

Cutaneous findings identical to those in PCT, with similar skin fragility, erosions and blisters, but without porphyrin overproduction, have been reported in patients undergoing hemodialysis (25) and also in those exposed to certain drugs, e.g. furosemide, tetracycline, nalidixic acid, naproxen, ketoprofen and cyclosporine (26, 27). The term pseudoporphyria has been used to describe these conditions, since most of the patients have normal porphyrin profiles. A similar condition may occur after prolonged use of tanning beds (28-30).

Clinical findings and diagnosis

Skin fragility is the first and dominating skin sign in PCT, with a later appearance of blisters, erosions, crust and milia on sun-exposed sites, such as the dorsa of the hands. The tense bullae are not surrounded by inflammation and are usually filled with a clear fluid, although haemorrhagic blisters sometimes occur. It should be remembered that in HIV- and HCV-infected patients the blister material and erosions are highly contagious. Erosions and collapsed bullae later become crusted and heal slowly, leaving atrophic scars, milia and areas of hypo- and hyperpigmentation. The skin fragility is seen in virtually all patients, and its absence provides strong evidence against PCT. Hypertrichosis and hyperpigmentation may appear but sclerodermoid changes are rare and only seen in long-standing untreated patients (1, 2, 31).

The diagnosis must be confirmed by thorough biochemical investigations, including examination of porphyrins in urine, stool and blood. Porphyrin profiles are particularly essential in differentiating PCT in adults from two other less common types of porphyria – variegate porphyria and hereditary coproporphyria – otherwise clinically indistinguishable from PCT (1, 2, 31).

Laboratory tests should include a complete blood count, serum iron and total iron-binding capacity, ferritin, liver enzymes and fasting blood sugar. Hepatitis C should always be excluded (31).

Table I. *Clinical findings*

Skin fragility
Blisters and bullae on light-exposed areas
Erosions, crusts, scars, milia
Facial hypertrichosis, usually mild,and hyperpigmentation, may occur
Sclerodermoid plaques in longstanding cases

Referral

Individuals with suspected or confirmed liver disease such as lupoid hepatitis, cirrhosis, viral hepatitis and hepatocellular cancer should always be referred to a department of gastroenterology or hepatology before any other specific treatment is initiated (31).

Table II. *Important investigations to perform*

Liver transaminases
Iron
Serum ferritin concentration
Transferrin saturation
Hepatitis B and C serology
HIV infection when applicable
Full investigation of any underlying liver disease in individual cases
With liver biopsy, ultrasound, s-alfa-fetoprotein
The enzyme URO-D in erythrocytes to verify the PCT form and to differentiate from other porphyrias.
HFE gene (when transferrin saturation > 65%, s-ferritin > 400 µg/l)

Therapeutic considerations

Patient education is an essential part of the management of the condition. Patients should always be advised to avoid all known porphyrinogenic agents such as alcohol, oestrogens, iron supplementation, and to avoid sunlight and use a physical sunblock. They should be reminded that ordinary sunscreens usually do not help.

PCT responds favourably to either of two specific treatments ineffective in other cutaneous porphyrias, namely depletion of body iron stores and prolonged low-dose oral chloroquine (or their combination), which produces prolonged clinical and biochemical remission in most patients irrespective of the type of PCT.

Results of phlebotomy therapy

Phlebotomy therapy was first introduced by Ippen (32), who performed serial bleedings, removing 500 ml of blood, first weekly and later monthly, until haemoglobin fell to mild anemic values. Iron depletion is effective even in patients with a normal iron load. Phlebotomy leads to remission by reversing the inactivation of URO-D, while replacement of iron leads to relapse (1, 2). One unit of blood is removed by venesection every one or two weeks until the transferrin saturation approaches 15% or the hemoglobin falls to <110 g/l. Serum ferritin measurements (<20 µg/l) can also be used to monitor the therapeutic effect. The aim of the therapy is to reduce iron stores to just below normal, and this effect should be the one primarily monitored, whereas porphyrin measurements are less relevant. Full remission often takes up to about six months and may then last for years (1, 2, 10, 33, 34).

Results of chloroquine treatment

The historical background to the therapeutic use of chloroquine for PCT has been reviewed elsewhere (35–40). Chloroquine can cause acute toxic reactions at the beginning of its administration. However, when this occurs, treatment does not have to be discontinued, as there will be no permanent damage. References to the therapeutic use of chloroquine in PCT first appeared in the late 1950s. Initial results were discouraging because of the acute toxic reactions which often followed when the drug was given in the usual doses for the common photodermatoses (41). The high-dose chloroquine regiment has therefore not been generally accepted. These adverse reactions included malaise, fever, headache, myalgia and abdominal pain. However, a combination with phlebotomy reduces or eliminates this adverse reaction and has proved safe and effective (37, 42, 43).

The concept of using low-dose chloroquine (hydroxychloroquine) therapy for several months to reduce the severity of the hepatotoxic effects in PCT was first suggested by Saltzer et al. in 1968 (44) and has since been used successfully to treat patients with PCT in whom phlebotomy may not be appropriate (36, 39, 43, 45). It is believed that chloroquine enhances porphyrin excretion by forming water-soluble complexes (1, 46).

Our choice of therapy

A combination of venesection and oral chloroquine is the fastest way to induce biochemical and clinical improvement (40, 43).

We give low-dose chloroquine phosphate 125 mg twice a week, combined with phlebotomy, 400 ml per week. The phlebotomy is given until hemoglobin has fallen to 110 g/l or serum ferritin values are <20 µg/l. The patient is checked every third month and kept on chloroquine phosphate until uroporphyrin levels are normal. Biochemical and clinical improvement may be noted within 3-6 months. Blistering disappears first and later skin fragility.

When biochemical values are normal again, the patient is checked once every year. If there are signs of biochemical recurrence, therapy is reinstituted even if the patient has no clinical symptoms.

The problem of relapse

The problem of relapse in PCT therapy merits special attention and published long-term results differ greatly (1, 5, 36, 39, 43). Remission periods range from 6 months to 10 years, depending more on the type of PCT being treated than on the therapeutic method. Some cases need repeated treatment every second or third year.

Table III. *Porphyrin excretion pattern*

Complete porphyrin excretion pattern in urine and faeces is needed to differentiate PCT from VP and HCP

Table IV. *Precipitating factors to avoid*

Sunlight and regular sunbed usage
Alcohol
Oestrogens, natural or synthetic (for oral contraception, postmenopausal symptoms or prostatic carcinoma)
Iron supplementation

Table V. *Treatment*

Phlebotomy 400 ml/week combined with low-dose chloroquine phosphate 125 mg twice weekly gives the fastest clearance of the biochemical abnormality.
Chloroquine alone or phlebotomy solely can be used when one of them is contraindicated

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Table VI. *Controls*

Follow urinary porphyrin excretion, liver transaminases och serum iron at 3 month intervals until normalization, thereafter once yearly.

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