Porphyria for the general physician

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Introduction

Most physicians will probably identify no more than one or two cases of porphyria during their career, but will have excluded the diagnosis in many more and thus have a high threshold for contemplating the diagnosis. It is an increasingly important diagnosis to make because prevention of attacks is essential, effective treatments are available, and family studies and medico-legal issues are of increasing relevance.

The porphyrias may be currently classified as primary (genetic) or secondary, with the former subdivided into neuropsychiatric, cutaneous or mixed.[1] Recent studies have clarified the biosynthetic pathway for haem and the regulatory steps involved. More importantly, analytic techniques have been improved and porphyrin precursors can now be accurately analysed using high-performance liquid chromatography, assays of the relevant enzymes are relatively straightforward and molecular genetic studies available for general use. The establishment of two supraregional assay (SAS) centres for porphyrins and the porphyrias has placed diagnostic and clinical facilities on a more professional basis. Table 1 outlines the genetic porphyrias and the clinical and diagnostic features.

Clinical issues

The acute porphyrias

The principal features of an acute porphyric attack are well described in relevant medical textbooks. This review will consider atypical features and current diagnostic challenges.

The clinical features of an acute attack are varied. The most common symptom is abdominal pain, which may be accompanied by neurologic and psychiatric symptoms (Fig 1). Muscle pain with weakness is also common and may progress to quadraparesis and respiratory paralysis. Mild sensory changes may accompany the predominantly motor neuropathy. Marked constipation, nausea and vomiting with hypertension or postural hypotension are additional features. With appropriate specific treatment, symptoms remit within a few days.

Hyponatraemia

Although hyponatraemia is a well-recognised feature of acute attacks and may precipitate the confusing rhabdomyolysis occasionally seen,[2,3] acute porphyria is not generally considered in the differential diagnosis of hyponatraemia. Two recent reviews of hyponatraemia[4,5] have not mentioned porphyria, although retrospective case-note review of patients with a delayed diagnosis will often highlight hyponatraemia with abdominal pain as the initial presenting feature.

Delayed diagnosis

There is frequently a delay in diagnosis of porphyria. A recent UK review[6] of 81 patients indicated a mean delay of six years in diagnosis from initial symptoms, with a maximum of 49 years! With the ready availability through the SAS of definitive diagnostic tests, the delay is largely due to a lack of both diagnostic awareness and appropriate laboratory requests.

Key Points

- **Awareness and consideration are essential in making/suspecting a diagnosis of the acute neuropsychiatric porphyrias**
- **Acute porphyria should be considered in the differential diagnosis of hyponatraemia, renal impairment and atypical psychiatric and neurologic disorders**
- **Accurate quantitation of porphobilinogen, δ-aminolaevulinate and porphyrins in laboratory samples is essential in confirming a diagnosis**
- **Recent developments in treatment and prevention strategies have considerably improved the quality of life of patients with porphyria**
- **Molecular genetics are not necessary in initial diagnosis, but are valuable in confirmatory investigations and in family studies**
- **Accurate biochemical diagnosis is crucial in cutaneous porphyria since acute porphyrias (variegate porphyria and hereditary coproporphyria) can cause skin signs indistinguishable from a non-acute porphyria (porphyria cutanea tarda)**
- **Porphyria cutanea tarda often reflects underlying liver disease or haemochromatosis**

Neuropsychiatric features

The acute porphyrias are also known as the neuropsychiatric porphyrias due to the neurological and occasional psychiatric features of a severe acute attack. Occasionally, patients with a primarily psychiatric diagnosis are referred for consideration of an underlying porphyria.[7] Because of the stigma associated with a psychiatric diagnosis, patients and their relatives prefer a diagnosis of porphyria to one of a primary psychosis. A careful study by Patience *et al*[8] indicated that, with the exception of anxiety disorder, schizophrenia, bipolar disorder and simple depression are no more common in the acute porphyrias than in a control population. The basis of the association of chronic anxiety with porphyria is unclear. Some studies consider it secondary to recurrent acute attacks but it is equally common in fully latent cases. The symptoms may be quite disabling and referral for assessment and treatment (eg cognitive behavioural therapy) can be helpful.

A recent report has highlighted the important relationship between epilepsy and the acute porphyrias.[9]

Screening tests

Previous laboratory screening tests for porphyria were unreliable with false-positive and false-negative rates approaching 50%.[10] More recent semiquantitative tests are more accurate, but a definitive conclusion requires quantitative assay for porphobilinogen (PBG) and δ-aminolaevulinic acid (ALA) in an early morning urine sample.[11] Certain drugs may interfere with screening tests, while assays of PBG alone may be unreliable in aged urine samples, may not reflect the clinical activity of the porphyria, would not identify Doss porphyria (due to PBG synthase defect) and may miss cases of secondary porphyria (eg lead poisoning).

Renal complications

Renal complications of acute porphyria are recognised in the porphyria literature but nephrologists rarely consider them in the differential diagnosis of chronic renal disease. A recent update series on renal failure in this journal failed to mention porphyria.[12] Hypertension and analgesic nephropathy are not infrequent in porphyrics, but a specific tubulo-interstitial nephritis is also well recognised.[13,14] This is often accompanied by a significantly reduced plasma erythropoietin (EPO); deterioration of the renal damage may be halted by appropriate therapy.[15] It is postulated that high levels of ALA are tubulotoxic. Assay of urinary ALA and PBG may be misleading or not possible in patients with chronic renal failure. Assays of plasma

Table 1. Clinical and diagnostic features of the porphyrias.

Diagnosis	Principal clinical features	Relevant enzyme	Inheritance	Diagnostic features
Doss porphyria	Abdominal pain	ALA dehydratase (PBG synthase)	AR	↑Urinary ALA and copro III Normal faecal porphyrins
AIP	Abdominal pain Motor neuropathy GI disturbances (Neuropsychiatric)	HMB synthase (PBG deaminase)	AD	↑ALA and PBG ↑Urinary porphyrins
CEP	Severe skin lesions Haemolytic anaemia	Uroporphyrin III synthase	AR	Normal ALA and PBG ↑Urinary and faecal porphyrins ↑Red cell protoporphyrins
PCT	Marked skin lesions	Uroporphyrin decarboxylase	(AD)[a]	Normal ALA and PBG ↑Urinary and faecal porphyrins, especially carboxylic porphyrias
HC	Neuropsychiatric features Vesicular skin lesions	Coproporphyrinogen oxidase	AD	↑ALA and PBG ↑Urinary and faecal copro III
VP	Neuropsychiatric features Vesicular skin lesions	Protoporphyrinogen oxidase	AD	Characteristic plasma fluorescence ↑Faecal protoporphyrins
EPP	Acute photosensitivity Mild anaemia	Ferrochelatase	(AD)[b]	↑Red cell and faecal protoporphyrin IX

AD = autosomal dominance; AIP = acute intermittent porphyria; ALA = δ-aminolaevulinic acid; AR = autosomal inheritance; CEP = congenital erythropoietic porphyria; EPP = erythropoietic protoporphyria; GI = gastrointestinal; HC = hereditary coproporphyria; HMB = hydroxymethylbilane; HP = hereditary coproporphyria; PBG = porphobilinogen; PCT = porphyria cutanea tarda; VP = variegate porphyria.
(AD)[a]: 10-20% of PCT cases are hereditary; most are due to hepatic damage in susceptible individuals.
(AD)[b]: co-inheritance of a ferrochelatase expression allele and severe ferrochelatase defect required for clinical expression.

PBG and ALA are thus more useful but detailed plasma and faecal analysis, often in combination with molecular genetic studies, may be necessary for a definitive diagnosis.

Malignant disease

A topic of current interest, malignant disease in porphyria, has recently been reviewed in detail by Palmieri *et al.*[16] The prevalence of hepatocellular carcinoma (HCC) is increased in patients with acute intermittent porphyria (AIP) and porphyria cutanea tarda (PCT). Interestingly, the cutaneous porphyrias are not accompanied by an increased incidence of skin malignancy. Of increasing importance is the management of common intercurrent malignancies in patients with acute porphyria. In the past, such patients have been denied the full range of appropriate treatments (eg oncoplastic reconstructive surgery for carcinoma of the breast). Many chemotherapeutic agents are putatively porphyrinogenic and patients have been denied their benefits for fear of precipitating acute attacks. This is a rare complication, especially in patients with latent disease and, with the ready availability of haem arginate, chemotherapeutic agents are not necessarily contraindicated. Occult malignancy itself may precipitate acute attacks in susceptible individuals and should be considered, particularly in late onset patients.

Molecular genetics

The identification, chromosomal localisation and cloning of the genes for the haem biosynthetic enzymes has been a major advance; the results of such studies have already entered routine clinical practice.[17]

An interesting finding is the large genetic variation in the individual porphyrias. For example, over 400 mutations have been identified for AIP and additional mutations are being regularly reported. This variation partly explains the clinical heterogeneity of AIP and also accounts for the consistent clinical pattern within members of an individual family. There is, however, no clear linkage between extent or site of mutation and clinical features. For these reasons, molecular genetics are not appropriate for a primary diagnosis but are invaluable for family studies and identification of latent cases, particularly in children. In a small percentage of cases the mutation may not be identified using current techniques. Genetic testing has potentially important effects on attitudes and motivation to change behaviour in the porphyrias.[18]

Management of porphyria attacks

Prevention of acute attacks

The prevention of acute attacks in susceptible individuals is a prime responsibility of the patient's medical attendants. The approach advocated by the Cardiff group of emphasising safe lists of drugs rather than to highlight 'unsafe drugs to be avoided' is proving clinically useful. In circumstances where there are no safe drugs (eg cancer chemotherapy, active tuberculosis) clinical decisions must be taken on relative risks. Patients in clinical and biochemical remission are less likely to relapse; monitoring of urinary ALA can usefully predict a potential relapse. The ready availability of haem arginate enables incipient or actual acute attacks to be rapidly treated.

Precipitating factors

Added to the list of therapeutic and over-the-counter drugs (eg antihistamines) which may precipitate acute attacks, illicit substance misuse should be avoided. Tobacco use appears to prolong acute attacks[19] and some tobacco smoke components are likely to be porphyrinogenic as cytochrome P450 inducers. Nicotine is probably safe, and nicotine replacement therapy can safely be used as a smoking cessation aid in porphyrics. Patients with the acute porphyrias should avoid chronic alcohol misuse which is traditionally associated with porphyria.[20] There is little evidence that moderate social drinking is harmful or that red wine is more porphyrinogenic than white, as claimed. Marijuana, amphetamines, cocaine and ecstasy have all precipitated attacks in susceptible individuals and patients should be appropriately advised.

Treatment of acute attacks

Treatment of an acute attack in a known patient is a clinical decision.[21] It is not necessary, and is indeed harmful, to delay

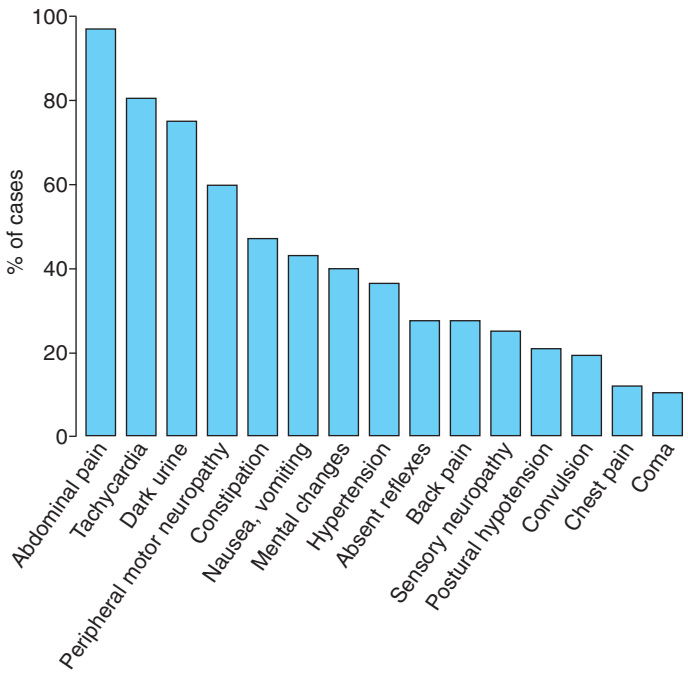

Fig 1. Frequency of signs and symptoms in acute porphyria (reproduced from Ref 1).

treatment while awaiting results of laboratory tests. It is important to ensure that the patient is not suffering from a non-porphyric cause for their abdominal pain. Inheriting the gene mutation for porphyria does not protect the patient from appendicitis, pancreatitis or ovarian cysts. High carbohydrate intake (ca 400 g/day) remains a useful adjunct to treatment of an acute attack and may alone abort an incipient attack. Recent experimental research indicates that carbohydrate and haem therapy are synergistic in reversing the biochemical changes in acute porphyria.[22] The introduction of haem arginate, now available on open prescription, has been an important advance in the management of acute attacks. It acts physiologically by inhibiting ALA synthase, the initial and rate-limiting enzyme in the haem synthetic pathway. It is, however, locally irritant and is best given via a central venous line. Administration in dilute albumin solution further reduces its local toxicity without affecting its efficacy. Very rarely, patients suffer allergic reactions to these infusions which poses a problem for patients with recurrent attacks. Use of hydrocortisone cover is effective in preventing these reactions.

Haem arginate. Regular monthly or weekly haem arginate infusions may be necessary in patients with recurrent attacks. Use of established central venous access with meticulous catheter care is essential; this approach has proved effective for several severely affected patients who have been maintained attack-free for at least five years.

Other pharmacological approaches. Recent studies have confirmed the value of haem oxygenase inhibitors in enhancing the efficacy of haem preparations,[23] but these compounds (tin porphyrins) are not recommended for current use.[24] Patients with regular premenstrual attacks may be helped by the use of gonadotropin-releasing hormone agonists and a six-month trial is worth pursuing.[25] The use of oral hormone replacement therapy to limit potential osteoporosis is not recommended as these preparations may precipitate acute attacks. Dermal preparations are the preferred therapeutic vehicle. Meticulous treatment of intercurrent infection and anaemia, and avoidance of stress will limit and prevent acute attacks. Reports, principally from Japan, of the beneficial effect of cimetidine are not well substantiated, and indeed this agent is a cytochrome inducer.[26] A recent report,[27] developing the observation that patients with anaemia have inappropriately low EPO levels, suggests that EPO therapy may be beneficial but there is a need for placebo-controlled trials of this approach.

It has long been known that the porphyrin precursors ALA and PBG are produced in the liver – hence the alternative classification of the neuropsychiatric porphyrias as hepatic porphyrias. The successful treatment of a severely affected patient with AIP by liver transplantation confirms this hypothesis and offers a potential treatment for patients with persistent disabling symptoms.[28]

Future prospects include the use of recombinant enzyme replacement and, in the longer term, gene therapy. The development of mouse models by gene knock-out technology is greatly facilitating our understanding of the pathogenic mechanisms and evaluation of novel treatments.[29–31]

Dual porphyria

Rare reports of PCT associated with one of the acute porphyrias have appeared. However, the notorious Chester porphyria (Dobson's complaint),[32] previously claimed to exhibit features of both AIP and variegate porphyria (VP), although never validated by modern diagnostic techniques, has recently been shown by molecular techniques to be straightforward AIP. No evidence for a protoporphyrinogen oxidase mutation characteristic of VP was found.[33]

Royal porphyria

The highly successful film and stage productions of *The madness of King George* have appeared to confirm a diagnosis of acute porphyria (VP) in selected ancestors. At best, the biochemical results have been doubtfully equivocal[34] and a recent biography[35] of George III suggests he suffered from recurrent attacks of cholelithiasis with bipolar disorder.[36] The dubious claims of his madness being due to porphyria are frequently distressing to our patients who constantly need reassurance on these issues.

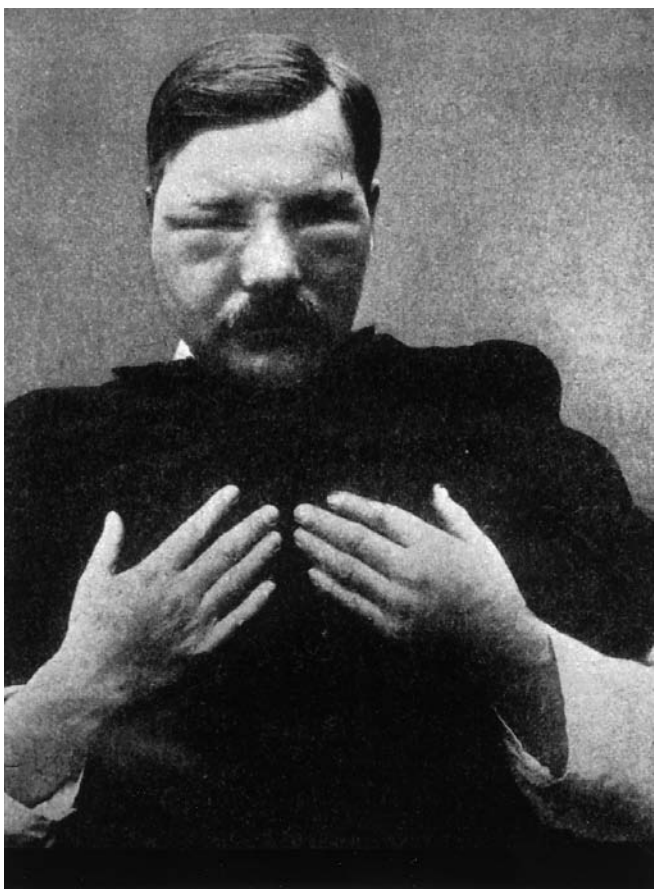

Fig 2. Dr Meyer-Betz proved that porphyrins cause light sensitivity by inducing this painful photosensitive reaction.[38]

The cutaneous porphyrias

Skin disease is a feature of most of the porphyrias because porphyrins become toxic when exposed to light. Photons of violet light (400–420 nm) electronically excite porphyrin molecules in the skin, which in their turn produce reactive singlet oxygen. This causes tissue damage directly and by other mechanisms, including complement activation, mast cell degranulation and activation of metalloproteinases.[37] The link between porphyrins and skin photosensitivity was first made in 1911 by Günther who identified increased concentrations of porphyrins in the urine of children with a mutilating light-sensitive skin disease (congenital erythropoietic porphyria (CEP)/Günther's disease). He proposed that the photosensitivity was caused by the porphyrins.

Proof came the following year when Dr Meyer-Betz, Chief Physician in Königsberg, East Prussia, injected himself with a porphyrin. The next day the sun came out while he was in a window seat on a tram journey and he took the opportunity to expose the right half of his face and his left hand to the sun, keeping the right hand as an unexposed control.[38] The oedematous porphyrin-induced photosensitive reaction was so painful that he required admission to his own ward (Fig 2).

Most cutaneous porphyrias present with fragility of exposed skin (particularly the backs of the hands) which is worse in summer, sometimes accompanied by tense blisters (bullae). Small white milia (tiny white cysts), scars and patches of abnormal pigmentation are the typical examination findings (Fig 3). Accurate diagnosis is vital because of the different clinical implications of several clinically indistinguishable cutaneous porphyrias. A random urine sample and either a plasma or a faecal sample should be sent to the laboratory.[39]

Porphyria cutanea tarda (PCT)

The most common of the 'bullous porphyrias' is PCT which, unlike the other porphyrias, is usually an acquired disorder – essentially a liver disorder which presents in the skin. It is caused by inhibition of the hepatic uroporphyrinogen decarboxylase enzyme by an endogenous inhibitor. This inhibitor forms only in the presence of iron and an oxidative environment, so liver pathologies associated with hepatic siderosis or free radical formation predispose to PCT.[40] Thus, in the UK, 20% of patients with sporadic PCT are found on investigation also to have subclinical genetic haemochromatosis (C282Y homozygosity), 10-15% are infected with the hepatitis C virus, about 30% of female patients are taking oestrogens for contraception or hormone replacement, and around 50% have excessive alcohol intake (Fig 4).[41] Hepatitis C serology, blood tests for iron status (serum ferritin) and liver function tests (LFTs) must be checked in all patients. Because of the link between liver disease and PCT, and the low but definite long-term risk of hepatocellular carcinoma, there should be a low threshold for further hepatological investigation. In the absence of severe iron overload, low-dose chloroquine (125 mg twice weekly) is an often overlooked but effective non-invasive treatment which works by facilitating porphyrin excretion by binding to it (daily chloroquine should be avoided because it can cause hepatic damage). Where there is iron overload, venesection is obviously the treatment of choice both for the liver damage and the porphyria. Eliminating triggers,

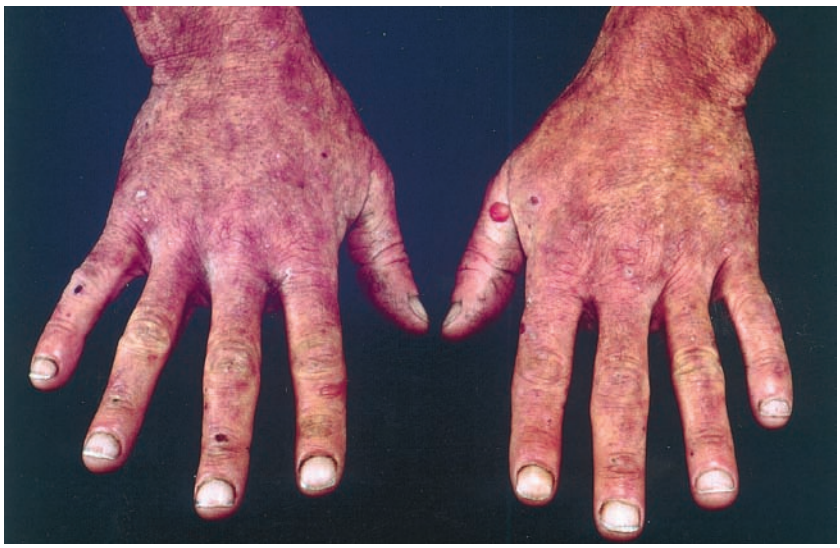

Fig 3. Blisters, erosions, pigmentation, scars and milia are typical features of a bullous porphyria. This patient had porphyria cutanea tarda.

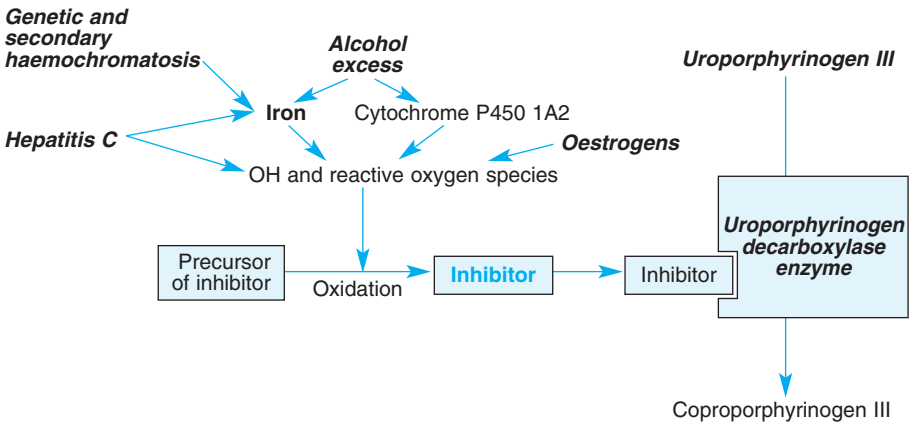

Fig 4. How predisposing factors relate to pathogenesis in porphyria cutanea tarda (OH = hydroxyl radical; UROD = uroporphyrinogen decarboxylase) (adapted from Ref 40).

particularly alcohol or oestrogens, may lead to resolution. However, in many patients the PCT is lifelong and long-term follow-up is needed to measure the urinary porphyrin concentration as a marker of relapse and to monitor LFTs.[41] Variegate porphyria and occasionally hereditary coproporphyria can present with skin disease indistinguishable from PCT yet, unlike PCT, these disorders can also cause acute porphyric attacks. This is why accurate biochemical diagnosis is so important in the bullous porphyrias for patients and their relatives. In addition, these diseases do not respond to antimalarials or venesection. Some patients with fragility and blistering in exposed skin do not have porphyria at all since 'pseudoporphyria' due to drugs (mainly non-steroidal anti-inflammatory drugs and tetracyclines) or haemodialysis presents like a bullous porphyria but without pathological increases in porphyrin concentrations.

Erythropoietic protoporphyria

Completely different problems are caused by erythropoietic protoporphyria (EPP). In this hereditary disease, severe burning pain occurs within minutes of exposing skin to spring or summer sunlight. The pain lasts for days, is difficult to control and is often accompanied by oedema (Fig. 5).[42] In EPP, the accumulated hydrophobic protoporphyrin causes pain and oedema because it localises to the endothelial lining of small blood vessels in the dermis, in contrast to the bullous porphyrias where porphyrin phototoxicity in dermal connective tissue causes the fragility and blistering. Protoporphyrin is also hepatotoxic and about 1% of EPP patients develop fulminant hepatic failure which usually requires liver transplantation.[43] EPP patients do not suffer acute porphyric attacks.

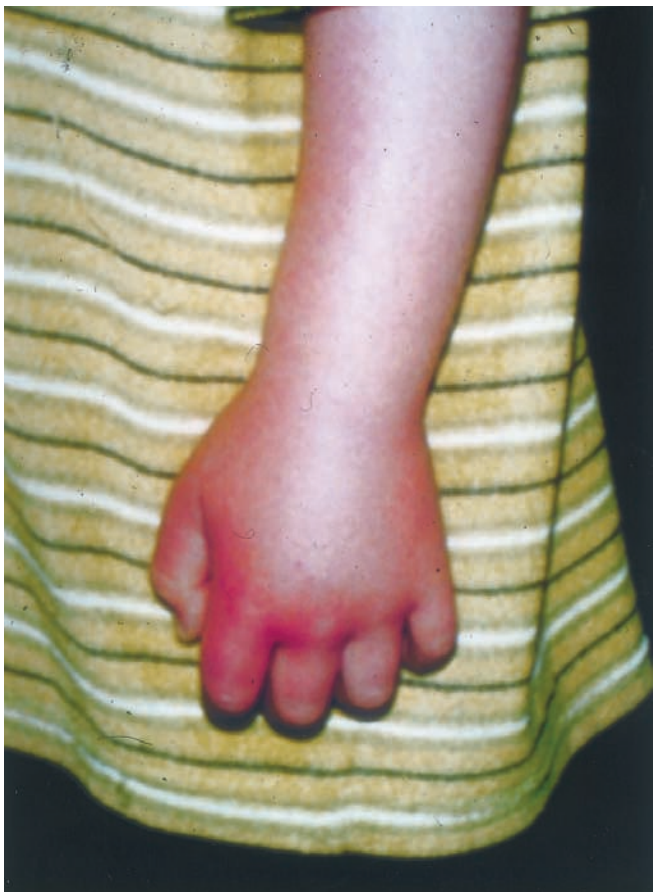

Fig 5. Oedema during a bout of sunlight-induced pain in a child with erythropoietic protoporphyria.

Congenital erythropoietic porphyria (CEP)

The first porphyria ever described, congenital erythropoietic porphyria (Günther's disease), causes severe photosensitivity with mutilating scarring and is a severe multisystem disease. Fortunately, it is rare. Patients now often survive into adult life because of improved management of secondary skin infections and haemolytic anaemia.[44] Bone marrow transplantation has recently been found to be curative.[45]

Sunscreens

PCT is the only cutaneous porphyria for which there is definitive and effective treatment, as outlined above. This makes effective physical protection against the pathogenic violet light (400–420 nm) critical in the other cutaneous porphyrias. Most sunscreens do not protect against violet light but opaque metal oxide-containing preparations are effective, particularly the 'Dundee sunscreen cream' (Tayside Pharmaceuticals, Ninewells Hospital, Dundee, Scotland). Clear window films which filter out violet light are also useful on car windows for EPP patients.

Conclusions

The cutaneous porphyrias (Table 2) present a complex interdisciplinary challenge for dermatologists, chemical pathologists, haematologists, hepatologists, clinical geneticists and general physicians. For these patients, the new world of 'multidisciplinary team working' needs to meet the old world where dermatologists are good physicians and physicians are good dermatologists.

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Table 2. Clinical features of the cutaneous porphyrias.

	Skin		
	Fragility, blisters	**Pain**	**Severe scarring**
Acute attacks			
Acute attacks can occur	VP, HC	–	–
No acute attacks	PCT	EPP	CEP

CEP = congenital erythropoietic porphyria; EPP = erythropoietic protoporphyria; HC = hereditary coproporphyria; PCT = porphyria cutanea tarda; VP = variegate porphyria.

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