British Journal of Dermatology 1999; **140:** 573–581.

The cutaneous porphyrias: a review

G.M.MURPHY, FOR THE BRITISH PHOTODERMATOLOGY GROUP
Photobiology Unit, Beaumont and Mater Misericordiae Hospitals, Dublin 7, Ireland

Accepted for publication 6 October 1998

Summary Many patients with cutaneous porphyria have curable or controllable disease; untreated porphyria may prove fatal. The genetic defects and mechanisms underlying porphyria are steadily being delineated, treatments have become more appropriate and genetic counselling is now more accurate. A summary of the basic diagnostic features, management and recent advances in the cutaneous porphyrias is presented, based on a workshop held by the British Photodermatology Group.

Key words: congenital erythropoietic porphyria, cutaneous porphyria, erythropoietic protoporphyria, porphyria cutanea tarda, review.

The porphyrias are caused by enzyme defects in haem biosynthesis leading to overproduction of porphyrins and their precursors (Table 1). Characteristic porphyrin profiles in plasma, erythrocytes, urine and stool allow the diagnosis to be made (Table 2). Tests for porphyria should be carried out by a laboratory accustomed to the technical methods and quality control is essential as many missed diagnoses are a consequence of false negative tests. A further cause of false negative results may result from deterioration of samples in transit, ethylenediamine tetraacetic acid plasma samples being more stable than serum samples.[1] The techniques depend on careful calibration of equipment and the use of standard solutions of porphyrins. Spectrofluorimetric scanning of plasma will detect all the cutaneous porphyrias during the symptomatic phase and is a useful screening test.[2] A spectrofluorimeter fitted with a red-sensitive photomultiplier must be used as this greatly increases the sensitivity of the test, enabling the diagnostic 625–627 nm peak in plasma of variegate porphyria (VP)[3] to be readily identified. Cholestasis and some drugs interfere with plasma fluorimetric assessment.

Porphyrin abnormalities, however, may also occur in lead poisoning, sideroblastic and haemolytic anaemia, iron deficiency, renal failure, cholestasis, liver disease and gastrointestinal haemorrhage, but only in rare cases of sideroblastic anaemia are there associated photosensitivity features.[4] Tyrosinaemia is associated with increased aminolaevulinic acid (ALA) levels.

Porphyrin molecules are ring structures which absorb visible light, generating excited states. Excessive concentrations of porphyrins exposed to daylight generate free radicals with consequent lipid peroxidation and protein cross-linking leading to cell membrane damage and death. The type of cellular damage depends on the solubility and tissue distribution of porphyrins.[5] Two main patterns of skin damage are seen in the porphyrias. Accumulation of water-soluble uroporphyrins and coproporphyrins leads to blistering which is seen in most of the cutaneous porphyrias, whereas accumulation of the lipophilic protoporphyrin is characterized by an immediate burning sensation in the skin on exposure to light, which may occur alone or be followed by swelling, redness, purpura and/or erosions, features typical of erythropoietic protoporphyria (EPP).

Clinical features

The porphyrias are most usefully classified as those with and without acute attacks (Table 3). Cutaneous features are not seen in acute intermittent porphyria (AIP) or the very rare ALA dehydratase (ALA-D) deficient porphyria.[6] EPP and Gunther's disease or congenital erythropoietic porphyria (CEP) are characterized by porphyrins produced mainly in the bone marrow; the remainder are primarily hepatic porphyrias (Table 3).

Porphyria cutanea tarda

Porphyria cutanea tarda (PCT) is the most common

Correspondence: Dr Gillian M.Murphy. E-mail: gillian@iol.ie
This report is based on a British Photodermatology Group workshop held in November 1994 and was contributed to by T.Cox (Cambridge), C.Darby (Dublin), H.du Peloux Menagé (London), G.H.Elder (Cardiff), J.Ferguson (Dundee), N.K.Gibbs (Dundee), J.L.M.Hawk (London), B.Johnson (deceased; Dundee), M.Moore (Brisbane), W.O'Connor (Rochester, MA, U.S.A.), F.O'Reilly (Atlanta, GA, U.S.A.) and R.Sarkany (Cambridge).

Table 1. The haem biosynthetic pathway

Glycine and Succinyl CoA			
⇓			
ALA synthase[a]	X-linked hereditary sideroblastic anaemia		
⇓			
Delta ALA			
⇓			
ALA dehydratase	ALA dehydratase deficient porphyria		
⇓			
Porphobilinogen (PBG)			
⇓			
PBG deaminase	AIP		
⇓			
Hydroxymethylbilane			
⇓			
Uroporphyrinogen III synthase	CEP		
⇓			
Uroporphyrinogen	⇒	**Uroporphyrin I & III**	
⇓			
Uroporphyrinogen decarboxylase	PCT		
⇓			
Coproporphyrinogen	⇒	**Coproporphyrin I & III**	
⇓			
Coproporphyrinogen oxidase	HC		
⇓			
Protoporphyrinogen			
⇓			
Protoporphyrinogen oxidase	VP		
⇓			
Protoporphyrin			
⇓			
Ferrochelatase and Fe^{2+}	EPP		
⇓			
Haem & Globin		**Haem & Apoprotein**	
⇓		⇓	
Haemoglobin		**Cytochromes**	

Enzymes controlling the porphyrin pathway are indicated in italics, the products are in bold, and the diseases resulting from deficiencies in enzyme activity are underlined. ALA, aminolaevulinic acid; AIP, acute intermittent porphyria; CEP, congenital erythropoietic porphyria, PCT, porphyria cutanea tarda, HC, hereditary coproporphyria; VP, variegate porphyria; EPP, erythropoietic protoporphyria. [a]Erythroid and ubiquitous isoenzymes are encoded by genes on the X chromosome and chromosome 3, respectively. Mutations in the former cause sideroblastic anaemia.

porphyria[7] with an estimated incidence of one in 70,000.[8] Presenting clinical features are listed in Table 4: these clinical signs are variable in severity. Diseases associated with PCT[9–18] are listed in Table 4. Patients present with hypertrichosis, or hirsuitism, hyperpigmentation, abnormal liver function or hepatocellular carcinoma. PCT may present in the context of haematological malignancy or β-thalassaemia. Skin fragility and erosions may be misdiagnosed for years as 'dermatitis'.

Figure 1 illustrates the classical appearance of PCT. Most PCT is acquired (type I) and is multifactorial in origin.[8] Sixty per cent of PCT patients are male, most ingesting excess alcohol; 40% are female and often on oestrogen-containing medication. Most patients with PCT are older than 40 years, and 66% have evidence of iron overload.[19] Almost 40% of PCT patients of northern European origin carry one or more alleles for haemochromatosis.[20] On screening patients with iron overload, PCT and haemochromatosis were found with a higher frequency than expected.[21] Both hepatitis C infection[12,13] and human immunodeficiency virus (HIV) infection[16] are now also firmly implicated in the precipitation of acquired PCT, with other viruses such as hepatitis B[14] and cytomegalovirus[15] more rarely implicated. PCT presenting in a young adult should lead to consideration of HIV infection as a cause; alternatively, familial PCT may be relevant.[22] Autoimmune disease[16] and haematological malignancy[18] are associated with PCT more often than expected.

Table 2. Diagnosis of porphyria

Porphyria	Enzyme	Urine	Stool	Plasma	RBC
PCT	Uroporphyrinogen decarboxylase	URO +++ COPRO + 7COOH III > I	ISOCOPRO ++ 7COOH	+	–
EPP	Ferrochelatase	Normal	PROTO +	+	Free PROTO ++
CEP	Uroporphyrinogen III synthase	URO I + COPRO I +	COPRO I +	+	URO I + COPRO I + PROTO +
AIP	PBG deaminase	[a]ALA +++ [a]PBG +++	[a]ALA + [a]PBG +	–	–
VP	Protoporphyrinogen oxidase	[a]ALA ++ [a]PBG ++ URO + COPRO ++	COPRO + PROTO ++ PORPH X +++	625–627 nm peak	–
HC	Coproporphyrinogen oxidase	[a]ALA ++ *PBG ++ COPRO ++ URO +	COPRO +	+	–
ALA-D	ALA dehydratase	ALA +++ COPRO III	–	–	PROTO Zn
Tyrosinaemia	ALA dehydratase	ALA	–	–	–
Iron deficiency	Ferrochelatase	–	–	–	Zn PROTO ++
Lead poisoning	ALA dehydratase Coproporphyrinogen oxidase Ferrochelatase	ALA +++ COPRO ±	–	–	Zn PROTO +

PCT, porphyria cutanea tarda; EPP, erythropoietic protoporphyria; CEP, congenital erythropoietic porphyria; AIP, acute intermittent porphyria; VP, variegate porphyria; HC, hereditary coproporphyria; ALA, aminolaevulinic acid; ALA-D, ALA dehydratase deficient porphyria; HEP, hepatoerythrocytic porphyria; PBG, porphobilinogen; URO, uroporphyrin; COPRO, coproporphyrin; ISOCOPRO, isocoproporphyrin; PROTO, protoporphyrin; RBC, red blood cells; +, positive; [a]during acute attack.

Familial PCT (type II) is found in 10–20% of cases; it is autosomal dominant with incomplete penetrance, and 90% of gene carriers are asymptomatic. Many of the factors relevant in sporadic PCT may contribute to disease expression which is, nevertheless, incompletely understood. If a child inherits uroporphyrinogen decarboxylase deficiency from each parent, a severe mutilating type of porphyria presenting in childhood may occur: hepatoerythrocytic porphyria.[23] Within this form of PCT numerous different mutations have been described, and many familial cases are, in fact, heteroallelic with a different mutated allele inherited from each parent; some children are homoallelic.

Table 3. Classification of the porphyrias

Acute porphyria	Non-acute porphyria
ALA-D deficient porphyria	Porphyria cutanea tarda
Acute intermittent porphyria	Erythropoietic protoporphyria[a]
Variegate porphyria	Congenital erythropoietic porphyria[a]
Hereditary coproporphyria	

ALA-D, aminolaevulinic acid dehydratase; [a]erythropoietic porphyrias; the remainder are hepatic.

PCT baseline investigations are listed in Table 4. Therapeutic protocols are listed in Table 5.[24–40] Venesection should be carried out weekly if possible until iron stores are bordering on deficient. Absolute avoidance of alcohol is necessary for all patients, but oestrogens may be continued if there are sufficiently strong clinical indications. Erythropoietin may enable utilization of body iron stores without the need for concomitant phlebotomy. Interferon alpha, used in progressive hepatitis C liver disease, may improve the symptoms of PCT.

Erythropoietic protoporphyria

EPP is the most common childhood porphyria, usually evident by age 2 years.[41] Clinical suspicion of EPP should be alerted by a history of screaming or skin pain on going outdoors. Erosions on the face, healing with scars, or waxy thickening of the skin of the nose

Table 4. Clinical features, disease associations and baseline investigations in porphyria cutanea tarda (PCT)

Clinical features of PCT
Skin fragility
Blistering
Sores
Scarring
Milia
Hypertrichosis[9]
Scarring alopecia
Hyperpigmentation
Hypopigmentation
Scleroderma[10]
PCT-associated disorders
Alcoholism
Haemochromatosis[11]
β-Thalassaemia
Diabetes mellitus
Hepatitis C[12,13]
Cytomegalovirus infection[14]
Human immunodeficiency virus (HIV) infection[15]
Lupus erythematosus[16]
Renal failure
Dialysis
Hepatocellular carcinoma
Haematological malignancy[17,18]
Investigation of PCT
Fresh random urine, and/or plasma for screening
Quantitative porphyrin analysis (24 h urine, plasma, stool) if screen positive
Full blood count, renal and liver function tests
Screen for hepatitis A, B and C
Autoimmune screen
Serum ferritin
Serum iron and total iron-binding capacity
Blood sugar
HIV screen if indicated
Ultrasound of liver
Liver biopsy[a]

[a]May be indicated clinically for diagnostic or treatment monitoring purposes.

and knuckles may be present (Fig. 2). Table 6 summarizes the clinical features in EPP: mild abnormalities of liver function may be detected in about 10%,[41] and liver failure affects about 5%. Early diagnosis is necessary as liver transplantation may be life-saving,[34] although patients continue to have symptoms of EPP.[42] One report links alcohol excess with EPP liver disease.[43] Protoporphyrin-containing gall stones may develop at an early age. If liver function is progressively abnormal, liver biopsy may be indicated. Disproportionately high plasma compared with faecal protoporphyrin levels and rising red cell protoporphyrin concentrations may be harbingers of liver failure.[33]

Many patients with EPP have an apparent mild anaemia with a microcytic hypochromic blood film. However, on electron microscopic examination, iron deposition in erythroblasts has been found, together with ring sideroblasts, implying inability to produce haem due to partial ferrochelatase deficiency.[44] If iron is administered in this situation, however, it may exacerbate the porphyria, possibly by derepressing erythroid ALA synthase and so increasing porphyrin synthesis. Symptomatic frank iron deficiency, however, requires treatment.

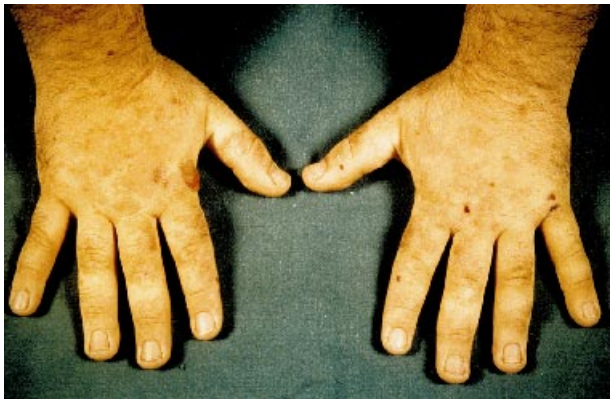

Figure 1. Typical appearance of porphyria cutanea tarda, with blistering, erosions, scarring, milia and hyperpigmentation on the dorsum of the hands.

If patients with EPP need surgery, theatre personnel must be warned about the potential hazards of exposure of internal organs to prolonged visible light; severe burns to internal organs and wound dehiscence may occur,[45] particularly with liver transplantation when porphyrin levels are very high because of liver failure, and theatre lights should be shielded to reduce radiation of 380–420 nm. In a few instances, a postoperative neurological syndrome with peripheral neuropathy and confusion has developed,[42,46] where patients required prolonged mechanical ventilation and had persisting motor defects. Intermediate survival rates (up to 5 years follow-up) show survival rates comparable with the general transplant population.[42] Disease may recur in the graft.

Therapeutic options[28–34] are summarized in Table 5. Perhaps the most innovative is the use of narrow-band ultraviolet (UV) B TL-01 lamps with an output at 312 ± 2 nm to induce UV tolerance in patients with EPP. With this technique, a protection factor of 8 may be obtained.[32] Although β-carotene is widely used, robust data on its efficacy are lacking.

Congenital erythropoietic porphyria

CEP is very rare and is characterized by very severe

Table 5. Therapeutic protocols for the porphyrias

Porphyria	Treatment	Indication/effect	Current status
PCT	Venesection: 500 mL weekly or twice monthly[24]	PCT and iron overload	Remission in 6–12 months
	Chloroquine 125 mg twice weekly[25]	PCT	Remission in 6–12 months
	Erythropoietin[26]	PCT and anaemia	Remission in 6–12 months
	Interferon[27]	PCT + HCV progressive liver disease	May be effective
EPP	β-Carotene[28]	Free radical scavenger	Possible efficacy
	N-acetylcysteine[29]	Free radical scavenger	Not effective
	Cysteine[30]	Free radical scavenger	Possible efficacy
	Antihistamines[31]	Reduce weal/flare	Marginal efficacy
	TL01 therapy[32]	Skin tanning and thickening	Protection factor of 8 is useful
	Cholestyramine[33]	Increases protoporphyrin excretion	Reserve for incipient liver disease
	Liver transplantation[34]	Restores normal liver function	EPP symptoms continue post-transplant
CEP	Oral superactivated charcoal[35]	Reduced enterohepatic porphyrin circulation	Sometimes effective
	Hypertransfusion	Reduction of porphyrins	Temporary effect
	Splenectomy[36]	Reduces haemolysis and platelet consumption	Sometimes effective; may be temporary
	Bone marrow transplantation[37]	Removes main site of porphyrin production	Requires suitable donor
VP, HC, AIP	Haem arginate 4 mg/kg per day intravenously[38]	Acute attack: suppresses ALA PBG production	Treatment of choice
	Carbohydrate loading oral/nasogastric/intravenous	Acute attack	If above not available
	LHRH agonists[39]	Premenstrual attacks	May prevent attacks
	Tin protoporphyrin[40]	Repress haem synthesis	Use with haem arginate; causes photosensitivity

PCT, porphyria cutanea tarda; EPP, erythropoietic protoporphyria; CEP, congenital erythropoietic porphyria; VP, variegate porphyria; HC, hereditary coproporphyria; AIP, acute intermittent porphyria; LHRH, luteinizing hormone releasing hormone; HCV, hepatitis C virus; ALA, aminolaevulinic acid; PBG, porphobilinogen.

photosensitivity with phototoxic burning and blistering leading to mutilation of light-exposed parts (Fig. 3);[47] hypersplenism and haemolytic anaemia with thrombocytopenia are also often severe. Milder variants have been described with onset in adult life.[48] Thrombocytopenia has been a presenting feature of several of the adult cases, beginning years before cutaneous signs similar to those of PCT.[36] Management of severely affected individuals means absolute avoidance of solar radiation of 360–500 nm for skin and eyes; scleromalacia perforans is an avoidable ocular complication. Other therapeutic measures[35–37] are summarized in Table 5. Bone marrow transplantation may correct the basic defect. Three recent reports show variable outcomes: the first child to receive a bone marrow transplant died of cytomegalovirus infection 11 months after transplantation,[37] the second required two bone marrow transplants from an HLA-identical sibling but was well 12 months post-transplant,[49] and the third achieved successful transplantation following umbilical blood stem cell bone marrow transplantation: follow up after 10 months indicated successful transplantation and effectively a cure.[50] Gunther's disease is variable in severity, and thus, the morbidity and risks of the procedure should be carefully considered in each case. Twenty-two different CEP mutations have been described to date. Prenatal diagnosis is now available, enabling diagnosis by amniocentesis at 16 weeks,[51] and thus, families should receive genetic counselling.

Acute cutaneous porphyrias

In many patients carrying genes for acute porphyria, the disease remains latent and presents no clinical evidence. Cutaneous features of VP and hereditary coproporphyria (HC) may be subtle, but are identical to those of PCT (Table 4). VP is not a rare disease: it may be latent or mild in expression. Less than 10% of patients with overt acute porphyria will develop an acute attack, the features of which are summarized in Table 7. Acute porphyria presents after puberty. The exact biochemical basis of acute attacks is unknown,[52] although many of the implicated drugs induce cytochrome P-450, and by diverting haem towards the cytochrome pathway lead to lack of feedback repression on ALA synthase and overproduction of porphyrins and their precursors. Polypeptide levels increase during acute attacks and may mediate some of the symptoms.[53] Other causes include infection, pregnancy, hormonal fluctuation, excess alcohol consumption and

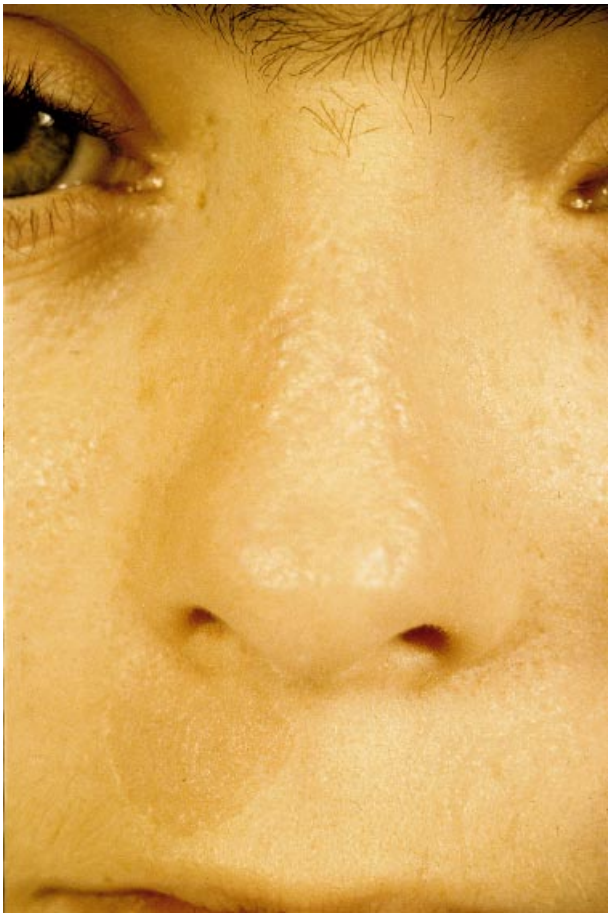

Figure 2. Waxy thickening and subtle linear scarring on the nose in erythropoietic protoporphyria; a shallow circular scar in present on the upper lip.

catabolic states. Drugs thought to be unsafe are listed in the *British National Formulary*.[54]

Acute attacks are less frequent than in AIP. Families should be screened for VP and HC to identify those at risk from acute porphyria. Metabolite measurements are generally normal in both conditions before puberty. After the age of 15 years, a specific plasma fluorescence test with a diagnostic peak at 625–627 nm[3] may be used to confirm the diagnosis in VP, and screen family members. In VP, a negative plasma fluorescence test confers a 1 in 8 risk for a first-degree relative over age 15 years, and a second-degree relative has only a 1 in 22 risk—close to the certainty achieved in measuring protoporphyrin oxidase activity.[55] Considering that the alternative risk is 50% within the family, this improvement in risk assessment is helpful in genetic counselling.

The gene encoding protoporphyrinogen oxidase has been identified, cloned and sequenced, and several different mutations have been described, including one common mutation, R59W, in South Africa. This confirms the founder hypothesis, with most cases of VP in South Africa thought to be descended from a seventeenth century Dutch immigrant.[56] DNA tests are becoming available for screening families for VP and HC and are applicable at all ages.[57] Homozygous VP, where a child inherits a VP mutation from each parent, is now well characterized, presenting in childhood, with short stature, moderately severe photosensitivity and clinodactyly.[58,59]

HC most frequently presents with attacks of acute

Table 6. Clinical features, complications and baseline investigations in erythropoietic protoporphyria (EPP)

Clinical features of EPP
Skin pain or burning in sunlight
Erythema
Swelling
Purpura
Sores on light-exposed areas, mainly face
Scarring—shallow circular or linear
Waxy thickening of skin
Complications of EPP
Anaemia
Gallstones
Liver failure
Investigations of EPP
Ethylenediamine tetraacetic acid blood
Quantify porphyrins in red cells, differentiate zinc and free protoporphyrin
Full blood count
Iron, total iron binding capacity, ferritin
Liver function tests once a year if normal
Ultrasound/computed tomography/magnetic resonance imaging of liver
Liver biopsy[a]

[a]May be needed if there are diagnostic difficulties or where progressive liver disease occurs.

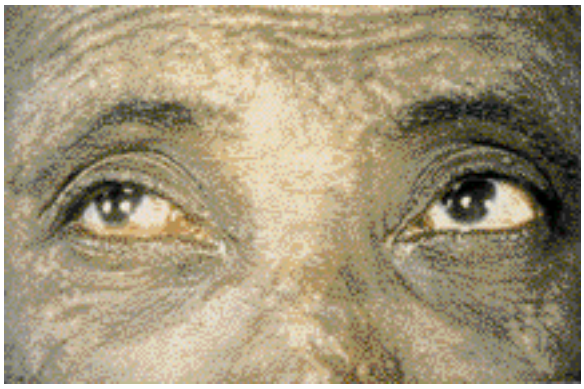

Figure 3. Scarring and hypopigmentation of the face with incipient scleromalacia perforans of the right eye in congenital erythropoietic porphyria.

Table 7. The acute attack

Gastrointestinal	Neurological	Cardiovascular
Abdominal pain	Peripheral neuropathy	Tachycardia
Nausea	—motor and sensory	Hypertension
Vomiting	Muscle and back pain	
Constipation	Ascending paralysis	
Diarrhoea	Paraesthesia	
	Encephalopathy	
	Anxiety	
	Psychosis	
	Coma	
	Seizures	
	Proximal neuropathy	
	Bulbar palsy	
	Aphonia	
	Dysphagia	
	Respiratory paralysis	

porphyria; the skin signs in HC may be absent or PCT-like. Homozygous HC and a related condition called harderoporphyria have been described,[60] in which one of the porphyrins excreted resembles that found in high concentration in the rat harderian gland. Homozygous HC may present in childhood with severe photosensitivity, such as CEP.

Therapy for acute porphyria is summarized in Table 5. Haem arginate[38,54] curtails the duration of acute attacks, and tin protoporphyrin[40] is an experimental treatment which acts by feedback repression of the haem pathway.

Homozygous and mixed porphyrias

Patients present rarely with cutaneous porphyria that does not fit into the above categories. The profile of porphyrins may indicate the diagnosis, particularly if the red cell protoporphyrin is elevated, as occurs in all the homozygous porphyrias. Screening the parents biochemically may suffice, but where doubt exists, measurement of enzyme activity will indicate profound suppression of the enzyme activity in the proband, and the parents may have enzyme activity of 50% that of normal. Rarely, PCT and VP may occur together, as may a variety of dual porphyrias.

Genetics

The genes encoding the enzymes causing porphyria have all recently been characterized.[61–71] Most porphyrias are inherited as dominant traits, with clinical expression in heterozygotes. However, penetrance is low so that not all who inherit the genetic defect manifest disease symptoms.[72] Family studies in EPP show that fewer than 10% of gene carriers have clinically overt disease.[73] CEP and ALA-D deficient porphyria are inherited recessively; the other porphyrias are dominantly inherited, although EPP may be recessive,[74] and liver failure has been associated with recessive inheritance.[75] Gene carriers with latent disease in family studies may be identified by measuring enzyme activity. In some families, DNA analysis may be the only way of identifying carriers with certainty. In CEP, molecular analysis has shown that most patients have different mutations on each allele and are thus compound heterozygotes; correlation of genotype and phenotype suggests a link between mutation type and disease severity.[76]

Management of the porphyrias

General measures helpful for all patients include full explanation of the nature of the disorder and provision of written patient information. Sources of information include major centres dealing with porphyria. The severity of the disease determines how much light restriction should be advocated. Reduction of light exposure by wearing clothing, particularly hats and gloves, greatly reduces damage to skin. Sunglasses excluding UV and visible light in the blue region should be worn, as conjunctival damage and even scleromalacia perforans may occur with severe porphyria. Standard total sunblocks are ineffective against visible light. Opaque sunblocks are required but are not usually acceptable. Window glass does not protect against visible light. Avoidance of outdoor activities is recommended and career guidance should advocate an indoor occupation. Genetic counselling should be available for those with inherited disease. Patient follow-up is advocated, particularly in those at risk of long-term complications, and to facilitate access to genetic and therapeutic information.

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