European Dermatology Forum

Guidelines in classification, diagnosis, and treatment of the photodermatoses

7. Endogenous: The (cutaneous) porphyrias

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1 - Definition

The porphyrias are a group of infrequent metabolic diseases caused by partial deficiencies of the activity of 7 sequentially acting enzymes in the biosynthesis pathway of haem. They are inherited diseases with the exception of sporadic Porphyria cutanea tarda. (PCT Type I) the most frequent form of porphyria. PCT type is the. result of inactivation of hepatic Uroporphyrinogen-decarboxylase (URO-D) enzyme.

2 - Pathogenesis

The result of these enzyme deficiencies or inactivation is the accumulation of intermediate metabolites in the pathway, the porphyrin precursors or porphyrins in tissues and their excess excretion in urine or stool.

The haem biosynthesis pathway includes 8 enzymes. Each enzyme deficiency correlates with one form of Porphyria except for the first one – (™ - amino levulinic acid synthase - ALA-S) causing X-linked sideroblastic anemia. The deficiency of second and third enzymes – ALA dehydratase and PBG deaminase – are related with two clinical pictures – ALA dehydrase porphyria (ADP) and Acute Intermitent Porphyria (AIP) – the acute porphryias with neurovisceral manifestations and no photosensitivity. These two forms of porphyria are out of the scope of these guidelines. From the fourth enzyme onwards photosensitivity manifestations are the main manifestations of the so called cutaneous and mixed porphyrias – associated to neurovsiceral symptoms - which include : Congenital erythropoietic porphyria (CEP), Porphyria Cutanea Tarda / Hepatoerythropoietic Porphyria (PCT / HEP), Variegate Porphyria (VP), Hereditary Coproporphyria (HCP) and Erythropoietic Protoporphyria (EPP). (Table1)

The presence of genetic defects does not correlate with clinical expression of the disease because the many different genetic mutations that can be found cause different levels of enzyme deficiency. On the other hand clinical expression depends on the action of secondary acquired and environmental factors. (Table2)

Clinical features

Classification

Porphyrias are classified in different ways:

1 – By location of the excess porphyrin production: **erythropoietic or hepatic**

2 – By clinical manifestations : **acute** (neurovisceral manifestations and no cutaneous photosensitivity), **cutaneous** (photosensitivity) or **mixed** (photosensitivity + neurovisceral manifestations)

Considering the scope of this guideline of photodermatoses the following clinical forms will be considered

1. - Erythropoietic porphyrias . Congenial erythropoietic porphyria (CEP) and Erythropoietic Protoporphyria (EPP)
2. - Hepatic porphyrias : Porphyria cutanea tarda (PCT type 1 sporadic, PCT type 2 familial) , Hepatoerythropoietic porphyria HEP,Variegate Porphyria (VP) and Hereditary Coproporphyria (HCP)

Epidemiology – Incidence / Prevalence

Porphyria appears in individuals in all human races. The prevalence has been evaluated in a variable percentage of 0.5 – 10 per 100.000 in different populations.

Clinical penetrance of genetic defects is very low so that about 80 % of individual carriers of mutations will never present biochemical alterations or develop clinical symptoms. Only irrelevant enzyme activity reduction may be present.

Nevertheless high prevalence gives the possibility of appearance homozygous inheritance of defects without consanguinity and the appearance of rare “dual” porphyria forms with inheritance of two different defects in the same individual.

Photoinduced cutaneous Clinical manifestations

Specific clinical cutaneous photoinduced manifestations of the different forms are grouped in:

Chronic photosensitivity:

CEP

PCT / HEP

VP / HCP (mixed porphyrias)

Acute photosensitivity

EPP

Chronic symptoms are manifested by skin fragility with erosions appearing with minimal trauma and bullous photo-induced lesions. These lesions evolve to scarring and slowly progressing sclerodermiform skin transformation with mutilating lesions specially on acral areas as fingers , nose and ears. Scalp alopecia may appear

Acute photosensitivity is manifested with erythema, oedema and petechiae associated to skin tingling, burning and pain. upon light exposures evolving to peculiar skin thickening characteristic in EPP.

Ocular lesions may be present (scleromalacia) or even oral mucosal lesions. In CEP teeth discolouration is a specific clinical sign – erythrodontia – which appears as bright red flourescent under Wood's light illumination.

On the other hand in some cutaneous porphyrias one has to consider the association with exogenous factors or other disorders that may influence the clinical evolution of the disease. Specially in the most frequent form of cutaneous porphyria, sporadic acquired PCT type I, clinical manifestations are due to the action of drugs (e.g. oestrogens), chemical substances (Hexachlorobenzene), alcohol, iron overload, and viral infections (Hepatitis C HCV, or Human immunodeficiency virus, HIV).

An evident relationship has been established with the inheritance of Hemochromatosis genetic defects .

Hepatobilliary alterations may be frequently associated with PCT and EPP and patients PCT especially associated with HCV may be prone to develop hepatocarcinoma.

Also haematological disease can be associated together with hematological malignancies especially in late onset porphyria..

Treatment procedures as hemodialysis may initiate PCT manifestations.

Pregnancy may influence the evolution of PCT and EPP.

There have been a number of reports of coincidence of propyria with Lupus erythematosus or Dermatomyositis in the same patient.

Pathogenesis of photoinduced lesiones in porphyria is complex. Porphyrins are phototoxic reactive molecules. accumulation of uroporphyrin and protoporphyrin in tissues allows phototoxic reaction production upon light exposure. This phototoxicity is the basis of cutaneous lesions through the generation of oxygen reactive species , lipid peroxidation leads to lesions of membrane structures and degranulation of mastocytes, liberation of inflamation mediators, complement activation and increased collagen synthesis.

Diagnostic procedures

After a **clinical assessment** , this diagnosis should be confirmed by laboratory work-up.

Laboratory study should include **(1) Biochemical investigation (2) Enzyme**

activity determination and **(3)Genetic studies** in order to trace family carriers

of the defect, risk of those carriers of presenting disease and establishment of associated genetic defects and risk factors.

1 Biochemical studies

Biochemical investigation includes the study of porphyrin (uroporphyrin, coproporphyrin and protoporphyrin) and porphyrin precursors (aminolevulinc acid, porphobilinogen) in urine, faeces and blood -plasma and RBC (See Diagnostic algorithm (Fig 1). and plasma specific fluorescence.peaks demonstration (PCT, VP).

2 Enzyme activity determination. This determination is usually performed in erythrocytes or leucocytes.

3 Genetic studies

The search for the mutation responsible is advisable specially in severe clinical forms (CEP , HEP) or mixed porphyrias (VP , HCP) to trace carriers for genetic counselling and prevention of acute manifestations. Prenatal diagnosis has already been performed in cases of CEP.

It is also advisable to look for associated gene mutations in

PCT - Investigation of haemochromatosis (HEFE) Mutations

EPP - Investigation of Single-Nucleotide Polymorphisms of IVS3-48C alleles.

Treatment

Management of cutaneous lesions

1 Photoprotection (cutaneous and ocular) (For all cutaneous and mixed forms)

High protection broad band Sunscreens (up to 600 nm)

Adequate clothing and exposure behaviour

Organic glasses mounted in spectacles with upper, lower and lateral protection

Window glass protection with filtering films (yellow acrylate)

Attention to operating theatres illumination.

2 Avoidance of skin trauma

Management of metabolic alterations

PCT

- Phlebotomy – 400-500 ml / every 14 days – 2 – 6 months to keep Hb levels between 100 –110 g/L. . Treatment of choice in patients with HEFE mutations. Not suitable for patients with tendency to anaemia or with cardio-vascular disease. Also not suitable for patients with cirrhosis due to the demand of augmented hepatic albumin synthesis. Not suitable for children in case of physical or emotional stress.

May be used during pregnancy. In this case iron supplementation should be avoided.

Monitoring includes determination of Hemoglobin concentration, Ferritin levels and serum iron binding capacity.

- Low-dose Chloroquine - 125 mg twice a week 6 – 12 months.

This approach is not advisable in case of HEFE mutations.

- Desferrioxamine -1,5 gr- 8-10 h. infusion – 5 days/week – weekly to halving the uroporphyrin excretion level, 2-3 weeks monthly to normalisation of uroporphyrin level, 1 week every 2-3 months as maintenance. Or 200mg/Kg in 500 ml saline once a week to halving uroporphyrin excretion and twice monthly up to normalisation and once every 2-3 months as maintenance.

- Other approaches - High-dose choloroquine (this could lead to liver failure in some patients) , IFN if associated to Hepatitis Virus C , HAART if associated to HIV infection, Alkalinisation, Vitamin E, Cimetidine(120).

In haemodialysis patients :

- Desferrioxamine 1,5 –4 g with haemodialysis

- Erythropoietin 20-50 U/Kg after haemodialysis or low-volume phlebotomies

50-10 mL/once or twice weekly.

- Plasmapheresis

- Plasma exchange

HEP

No specific treatment available but treatment as in CEP may be indicated.

VP / HCP

No specific treatment available but Phlebotomy as in PCT regimen may be applied

EPP

Photosensitivity

- Oral Betacarotene - 30 – 90 mg / day Infants 120-180 mg / day adults to keep plasma levels at 6-8 mg/L

- Other approaches - Oral Cysteine, Vitamin C, Cimetidine, NBUVB Phototherapy (only NBUV is evidence based)

Liver protoporphyrin deposition and hepatic disfunction

- Cholestyramine, RBC transfusions, Exchange transfusions, Intravenous hematin, Iron supplementation.

CEP

- High level transfusions (attention to iron overload)

- Oral activated charcoal – 60 gr three times daily

- Cholestyramine

- Hydroxyurea

- Splenectomy

- Hematin (late onset CEP) 3 mg./Kg. Daily for 4 consecutive days.

Transplantation

Severe forms of CEP and EPP Bone-marrow transplantation or Bone-marrow + Hepatic Transplantation. Liver transplantation is successful in the liver failure which is rarely associated with EPP, symptoms of EPP slowly recur. Liver failure in VP may also be treated by transplantation.

Other management recommendations

- Ocular protection in all forms is advisable

- Avoidance of triggering factors

Specially in the case of sporadic acquired PCT it is important to avoid triggering or aggravating factors as:

Drug, Alcohol, Hormones/ Oestrogens, Nutritional status - Starvation, Tobacco

Infections (HVC, HIV), Haemodialysis, Iron overload (HFE Mutations)

Chlorinated hydrocarbons

Follow up

Patients with prophyria should remain under control life-long clinically and biochemically. Levels of porphyrin excess excretion should be controlled periodically. Clinical evolution of lesions should be surveyed. In patients with

PCT

Serology for hepatitis virus – HVC / HIV – should be peridocallly checked. Abdominal ultrasound for early detection of hepatic cirrhosis development in HVC + patients for appearance of hepatocarcinoma.

EPP

Hepatic function and porphyrin profile changes for early detection of liver failure should be performed .(Decline of fecal protoporphyrin excretion and increase in urine coproporphyrin I > III ratio).

Gallstones formation

CEP and HEP

Follow-up of haemolytic anaemia

Tables

Table 1

The Porphyrias

Porphyria	Deficient enzyme – Heme biosynthesis	Porphyrin overproduction Erythropoietic / Hepatic	Clinical manifestations	Inheritance
	ALA-synthase			
ALA dehydratase deficiency prophyria (ADP))	ALA-Dehydratase	Hepatic	Acute neuro-visceral symptoms	Autosomal recessive
Acute intermittent Porphyria (AIP	PBG Deaminase	Hepatic		Autosomal dominant
Congenital erythropoietic poprphyria (CEP)	UROgen III Cosynthetase	Erythropoietic	Cutaneous Chronic Photosensitivity	Autosomal recessive
Porphyria cutanea tarda (PCt)	UROgen Decarboxylase	Hepatic		Autosomal dominant
Hepatoeritropoietic prophyria (HEP)		Hepatic Erythropoietic		Autosomal recessive
Hereditary coproporphyria (HCP)	COPROgen Oxidase	Hepatic	Acute neuro-visceral symptoms + Cutaneous Chronic Photosensitivity	Autosomal dominant
Variegate porphyria (VP	PPgen Oxidase	Hepatic		Autosomal dominant
Erythropoietic protoporphyria (EPP)	Ferrochelatase	Erythropoietic	Cutaneous Acute Photosensitivity	Autosomal dominant

Table 2

Cutaneous and mixed Porphyria – Genetic Background

Porphyria	Enzyme Ref. Nr.	Cromosomal location	Structure
Congenital erythropoietic porphyria (CEP)	URO-S EC4.2.1.75	10q25.3-q26.3	10 exons Hsk, 1+2B-10 Ery. 2A^{a}+2B-10
Porphyria cutanea tarda (PCt)	URO-D EC4.1.1.37	1p34	10 exons
Hepatoerithropoietic prophyria (HEP)			
Hereditary coproporphyria (HCP)	CPOX EC1.3.3.3	3q12	7 exons
Variegate porphyria (VP)	PPOX EC1.3.3.4	1q22	13 exons
Erythropoietic protoporphyria (EPP)	FECH EC4.99.1.1	18q21.3	11 exons

Evidence support of treatment options in Cutaneous prophyrias

(The British Association of Dermatologists guidelines for the management of skin disease – C.E.M. Griffiths – Br J Dermatol 1999;141:396-397)

Porphyria	**Treatment options**	**Level of recommendation (Class)**	**Level of evidence**
PCT	Phlebotomies	**A**	**1^{+}**
	Low-dose Chloroquine	**A**	**1^{+}**
	IFN(+Hepaptitis C infection)	**B**	**2^{++}**
	Deferoxamine(Hemodialysis)	**B**	**2^{++}**
	Erythropoietin(Hemodialysis)		
HEP	Treatment may be considered as in CEP	**C**	**2^{+}**
VP/HCP	Phlebotomy as in PCT	**C**	**3**
EPP	Iron supplementation	**D**	**3**
	Oral Betacarotene	**B**	**2^{+}**
	Oral Cysteine	**D**	**3**
	Vitamin C	**D**	**3**
	Cholestyramine	**D**	**3**
	RBC transfusions	**D**	**3**
	Hematin	**D**	**3**
	NBUVB phototherapy	**D**	**3**
	Bone marrow transplantation	**D**	**3**
	Liver transplantation	**D**	**3**

CEP	1-Biochemical normalisation	**D**	**3**
	High Level transfusions	**D**	**3**
	Oral activated charcoal	**D**	**3**
	Cholestiramine	**D**	**3**
	Hydroxyurea	**D**	**3**
	Splenectomy	**D**	**3**
	Bone marrow transplantation		

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Total references reviewed 3412

Selection general references

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