REVIEWS

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Clinical, Biochemical and Molecular Characteristics of the Main Types of Porphyria

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Abstract

Porphyrias are diverse disorders that arise from various inherited enzyme defects in the heme biosynthesis pathway, except for porphyria *cutanea tarda* (PCT), in which the enzyme deficiency in most cases is acquired. The biosynthetic blocks resulting from the defective enzymes are largely expressed either in the liver or bone marrow, the sites where the majority of heme is produced. Although the pathophysiologic mechanisms of the clinical manifestations of the porphyrias are not fully understood, two cardinal features prevail: skin photosensitivity and neurologic symptoms of intermittent autonomic neuropathy, acute neurovisceral attacks, and disorders of the nervous system. The primary diagnosis of the proband is based on biochemical testing, which is not always able to identify acute porphyrias, especially in asymptomatic family carriers when heme precursors and porphyrins excretion is normal, low-normal and high-reduced values of enzyme activity overlap, and hematological diseases responsible for abnormal blood cells distribution coexist. Molecular analysis of gene mutations responsible for each type of porphyria is the best diagnostic approach for symptomatic as well as presymptomatic gene carriers (**Adv Clin Exp Med 2016, 25, 2, 361–368**).

Key words: acute hepatic porphyrias, porphyria *cutanea tarda*, erythropoietic porphyrias.

Porphyrias are a group of hereditary metabolic disorders caused by deficiency of heme biosynthesis. They are inherited in an autosomal dominant or recessive fashion. Each type of porphyria results from reduced activity of a specific enzyme of the heme biosynthesis. Reduced enzyme activity results in the overproduction and increased excretion of toxic precursors and porphyrins which are responsible for presentation of various clinical symptoms – neurological or/and cutaneous – specific for each type of porphyria [1].

Heme Biosynthesis

The first as well as the 3 final steps of heme biosynthesis occur in the mitochondria while the other 4 are cytoplasmic. The first intermediate of the heme biosynthetic pathway is δ-aminolevulinic acid (ALA) formed by the condensation of glycine and succinyl CoA by δ-aminolevulinic acid synthase (ALAS). Two molecules of ALA are then condensed by ALA dehydratase (ALAD) yielding monopyrrole – porphobilinogen (PBG). Four molecules of PBG are combined by PBG deaminase (PBGD), also named hydroxymethylbilane synthase (HMBS), yielding linear tetrapyrrole – hydroxymethylbilane then converted to uroporphyrinogen III in the presence of uroporphyrinogen III synthase (UROIIIS) or spontaneously to uroporphyrinogen I. Decarboxylation of 4 groups of acetic acid to methyl groups of uroporphyrinogen III and I in the presence of uroporphyrinogen decarboxylase (UROD) yields coproporphyrinogen III and I. Coproporphyrinogen III oxidase (CPOX) then catalyses oxidative decarboxylation of coproporphyrinogen III to protoporphyrinogen IX. In the presence of protoporphyrinogen oxidase (PPOX) six atoms of hydrogen are removed from protoporphyrinogen IX to form protopor-

phyrin IX. The last stage of heme biosynthesis is the insertion of iron to the protoporphyrin IX ring and heme formation. The reaction is catalyzed by ferrochelatase (FECH).

Heme biosynthesis occurs mostly in the erythroblastic system (80%) and liver (15%) as well as in other tissues (5%).

The process is regulated by two tissue-specific isoenzymes encoded by 2 different genes – ALAS1 in the liver and ALAS2 in the erythroblastic system. ALAS1 activity is regulated *via* negative-feedback regulation by heme the – end product. ALAS2 is regulated by iron. Heme biosynthesis in erythroid cells is responsible for oxygen binding and transport (as hemoglobin). About 80% of heme produced in the liver is consumed by cytochromes which participate in the metabolism of corticosteroids and other drugs (as microsomal cytochrom P450) and electron transport in citric acid cycle (as mitochondrial respiratory cytochromes). The remaining 20% of heme produced in liver is consumed by tryptophan oxidation (as tryptophan pyrrolase), nitric oxide synthesis (as nitric oxide synthase), hydrogen peroxide metabolism (as catalase and peroxidase) and other processes [2, 3].

Classification of the Porphyrias

Porphyrias are classified according to clinical symptoms and biochemical defects at individual stages of heme biosynthesis caused by enzymatic deficiencies including tissues where abnormal heme biosynthesis occurs. Depending on the principal site of expression porphyrias are classified into hepatic and erythropoietic. Hepatic porphyrias include acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), ALA dehydratase deficiency porphyria (ADP) and porphyria cutanea tarda (PCT). Erythropoietic porphyrias include erythropoietic protoporphyria (EPP) and congenital erythropoietic porphyria (CEP). Depending on the clinical course of the disease we distinguish acute (AIP, VP, HCP, ADP) and cutaneous (non-acute) porphyrias (PCT, EPP, CEP) porphyrias. In two acute porphyrias VP and HCP cutaneous symptoms can also occur with or without acute attack [1].

Epidemiology Data

AIP is the most common type of acute porphyria in Europe. The prevalence of AIP in Europe is 1/75 000 inhabitants; in northern Sweden 1/1000 due to a founder effect [1, 4] and in Finland 3/100 000 [5]. AIP prevalence in Argentina is about 1/125 000 inhabitants [6]. VP is most frequently reported in South African Republic (1/300 inhabitants) due to founder effect [7]. VP prevalence in Finland is estimated at 2/100 000 inhabitants [8]; in Argentina at 1/600 000 [6]. HCP cases are very rare and no reliable epidemiological data are available. Up to date less than 50 HCP cases have been reported. ADP is extremely rare and so far up to 10 cases have been described [9].

Acquired PCT is the most common cutaneous porphyria: PCT prevalence in the European population is estimated at 1/5 000 – 25 000 inhabitants [10].

EPP prevalence ranges from 1/75 000 in the Netherlands to 1/200 000 in Wales [11, 12]. In Sweden the EPP prevalence is 1/180 000 [13], in Slovenia 1.75/100 000 [14]. CEP is very rare; to date approximately 150 cases have been reported [9].

The calculation of porphyria prevalence in Poland is based on the number of patients registered in the database of Laboratory of Porphyria at the Institute of Hematology and Transfusion Medicine. It is 7.2/100 000 inhabitants including: AIP 4.8/100 000, VP 0.7/100 000, HCP 0.09/100 000, EPP 0.1/100 000 and PCT 1.5/100 000 (accessed 09/04/2015).

Acute Hepatic Porphyrias

Clinical symptoms of acute hepatic porphyrias (AIP, VP, HCP, ADP) originate in the autonomic, peripheral and central nervous system. The clinical symptoms are non-specific and may imply diseases other than porphyrias. This impedes accurate diagnosis and delays treatment with impact on the course of attack and prognosis.

The onset of hepatic porphyria attack is provoked by a variety of precipitating factors such as: lipophilic drugs, chemical compounds particularly paint, varnish, organic solvents, pesticides, alcohol, stress, caloric deficiency, physical effort, endo- and egzogenic hormones as well as associated infections [15].

Acute porphyria attacks start with intense abdominal pain (85–95%), and muscle weakness (42––60%) followed by nausea and vomiting (43–88%), constipation (48–84%) or diarrhoea (5–12%), hypertension (36–54%), tachycardia (28–80%), limb, head, neck, chest pain (50–52%), mental symptoms (40–58%), convulsions (10–20%), fever (9–37%). No diagnosis, inaccurate recognition of porphyria or the administration of porphyrinogenic medication bring on a full-blown attack, paresis and paralysis of extremities and trunk muscles, respirato-

ry insufficiency (5–12%), encephalopathy, loss of consciousness and sometimes death [16].

In VP and HCP skin symptoms may occur with or without acute attack. Skin symptoms never occur in AIP and ADP [1].

Clinically overt hepatic porphyrias in children are extremely rare and occur mostly in severely affected homozygotes [17].

Acute Intermittent Porphyria

AIP is inherited in an autosomal dominant fashion with low clinical penetration. AIP is caused by mutations in the *HMBS* gene which lead to about 50% deficiency of HMBS (EC 4.3.1.8) which catalyzes the condensation of 4 PBG molecules to hydroxymethylbilane [3].

The 10 kb *HMBS* gene is located on 11q24.1––q24.2 chromosome and consists of 15 exons, 39–438 bp long. There are two promotors located in the 5'flanking region and intron 1 of *HMBS* gene. Due to tissue-specific alternative transcript splicing two transcripts are generated: housekeeping, including exons 1 and 3–15, and erythroid-specific, including exons 2–15. These two transcripts initiate erythroid-nonspecific and erythroid-specific isozymes of HMBS respectively. In most AIP patients HMBS deficiency occurs both in erythroid and non-erythroid cells (so called classical AIP). In about 5% of AIP patients HMBS activity is normal in erythrocytes but reduced in other tissues (so called non-erythroid AIP). Both types of AIP have the same clinical manifestations [18].

To date, 391 *HMBS* gene mutations responsible for AIP have been described. They are mostly mutations that affect both HMBS isozymes (classical AIP). The mutations within exon and intron 1 affected only erythroid-nonspecific enzyme variant (non-erythroid AIP). Most of them are point mutations with high heterogeneity except for mutation associated with so-called founder effect, e.g. mutation R1 98W identified in northern Sweden [4, 18, 19].

In about 90% of mutation carriers, porphyric symptoms never develop. Most of them present normal urinary excretion of heme precursors (PBG and ALA) and porphyrins. About 10% of carriers become symptomatic. Approximately 80% of AIP attacks occur in young women and often during premenstrual periods. During AIP attack urinary PBG and ALA excretion is high with PBG predominant. Urine porphyrins are also intense with high prevalence of uroporphyrins. Faecal porphyrins are normal or slightly elevated (Table 1) [20]. During acute attack, the urine of AIP patient is usually dark-red or dark-brown right immediately after urination or may darken due to sun exposure. Urinary amounts of PBG and ALA remain increased even during remission. During AIP attack HMBS activity in erythrocytes returns to normal [1, 3, 16, 21].

Variegate Porphyria

VP is characterized by approximately 50% deficiency of PPOX (EC 1.3.3.4) which catalyses the oxidation of protoporphyrinogen IX to protoporphyrin IX. The enzymatic defect is due to mutation in *PPOX* gene and is inherited in an autosomal dominant fashion with incomplete clinical penetration [22, 23].

The 8 kb *PPOX* gene encoding PPOX has been assigned to chromosome 1q22 and consists of 13 exons. Up to date 177 various *PPOX* gene mutations have been described. Among them most common are missens and frameshift mutations. VP mutations also show high heterogeneity with the exception of founder effect mutations e.g. mutation R5 9W in South Africa [7, 19].

Apart from acute attacks characteristic for all acute hepatic porhyrias, about 20% of VP patients may also present cutaneous photosensitivity with skin symptoms such as blisters, scars, erosions and hyperpigmentation. In about 60% of VP patients skin lesions are the only clinical manifestation. Acute attacks are less frequent in VP than in AIP; they are reported in less than 20% of patients with this type of porphyria [1].

Clinical VP symptoms include markedly increased faecal protoporphyrin and coproporphyrin with predominant protoporphyrin concentration. Urinary PBG, ALA and porphyrins are also increased, especially coproporphyrin. During remission urinary PBG, ALA and uroporphyrin may be normal, whereas faecal protoporphyrin and coproporphyrin levels remain elevated. Specific for VP is plasma fluorescence (max at 624–627 nm) (Table 1) [1, 16, 24].

Hereditary Coproporphyria

HCP is caused by mutations in the *CPOX* gene, which lead to about 50% deficiency of CPOX (EC 1.3.3.3), responsible for conversion of coproporphyrinogen III to protoporphyrinogen IX. HCP is inherited in an autosomal dominant fashion with low clinical penetration. As in other acute porphyrias, HCP is mostly latent before puberty [25, 26].

The gene locus encoding CPOX has been assigned to chromosome 3q12 and contains 7 ex-

ons. To date, 65 *CPOX* gene mutations have been described [19].

80% of HCP patients present only acute attacks similar to those in other acute hepatic porhyrias. Like in VP about 20% of HCP patients also present skin lesions. Skin lesions are the only clinical manifestation in 5% of HCP patients [1].

During HCP attack the main urinary and faecal biochemical abnormality is the markedly increased coproporphyrin, especially isomer III. PBG, ALA. Uroporphyrin values in urine are also increased (Table 1). During remission the urinary and faecal values may be normal [1, 16, 27].

ALA Dehydratase Deficiency Porphyria (ADP, Doss porphyria)

ADP is the rarest type of inherited porphyria. So far only six cases have been reported. ADP results from mutations in the *ALAD* gene. This results in the deficiency of ALAD (EC 4.2.1.2.4) which catalyses the condensation of two molecules of ALA to form one molecule of PBG. ALAD deficiency is inherited in an autosomal recessive fashion so ADP usually manifests in childhood in homozygotes with ALAD activity between 1–5% of normal value. A 50% decrease of ALAD is observed in asymptomatic heterozygotes. ALAD activity is inhibited by many chemicals or compounds, such as lead or succinylacetone. Clinical ADP symptoms resemble those characteristics which are connected to other acute hepatic porphyrias but present no photosensitivity or skin lesions [16, 28, 29].

The *ALAD* gene is located on 9q33.1 chromosome and consists of 12 exons. To date, 12 *ALAD* gene mutations responsible for ADP have been described [19].

In symptomatic patients urinary ALA and coproporphyrin values are markedly increased whereas other porphyrins are only slightly raised and the amount of PBG is normal. Zinc protoporphyrin in erytrocytes may also be higher (Table 1) [1, 16].

Cutaneus Hepatic Porphyria

Porphyria *Cutanea Tarda*

Porphyria *cutanea tarda* (PCT) is the most frequent of porphyrias due to partial deficiency of UROD (EC 4.1.1.37), which catalyses the decarboxilation of uroporphyrinogen III to coproporphyrinogen III. *UROD* gene is located on chromosome 1p34 and consists of 10 exons. To date 121 *UROD* gene mutations responsible for hereditary PCT have been described [19].

PCT is a chronic form of hepatic porphyrias that may occur either as sporadic (type 1, acquired) or familial (type 2, hereditary). Acquired (type 1) PCT is found in 75% of cases, mostly men. Patients with type 1 PCT have lower hepatic UROD activity, but normal erythrocyte enzyme activity. These patients have no *UROD* gene mutations. Hereditary (type 2) PCT occurs in 25% of cases. Patients with type 2 PCT have *UROD* gene mutations as well as decreased UROD activity in liver and erythrocytes. PCT type 2 is inherited in an autosomal dominant fashion with low clinical penetration [20, 30].

Risk factors for PCT include excessive alcohol intake, HCV, HBV and HIV infections, estrogens and hemochromatosis. They usually lead to hepatic iron overload, the main PCT causative factor [1, 20, 30].

Characteristic PCT symptoms are skin lesions on sun-exposed areas (backs of hands, neck and face) in form of blisters with serous fluid, erosions, scars and hyperpigmentation. The skin is coarse. PCT patients can develop cirrhosis and hepatocellular carcinoma [1, 16].

Symptomatic PCT patients have markedly higher urinary, faecal and plasma porhyrins, especially urinary uroporphyrin and heptacarboxylate porphyrin as well as faecal heptacarboxylate porphyrin and isocoproporphyrin. Urinary PBG is normal; ALA is normal or slightly increased. The best preliminary test for PCT diagnosis and differentiation from other skin-symptom porphyrias is the plasma porphyrin fluorescent assay with a characteristic peak at 618–620 nm (Table 1). In PCT remission urinary, plasma and faecal porphyrins return to normal. In symptomatic patients of type 1 and type 2 PCT hepatic UROD activities are reduced to about 25% of normal value. Erythrocyte UROD activity is normal in type 1 PCT and reduced by about 50% in type 2 either symptomatic or asymptomatic PCT [1, 16, 30].

Erythropoietic Porphyrias

The erythropoietic porphyrias (EPP and CEP) usually manifest cutaneous photosensitivity in early childhood but in rare cases they develop later in adult life [1, 30].

Erytropoietic Protoporphyria

EPP results from a partial deficiency of FECH (EC 4.99.1.1.), the last enzyme in the heme biosynthetic pathway which catalyses the insertion

Table 1. Biochemical and clinical presentation of porphyrias [1, 20, 36]

Characteristics of porphyria types				Biochemical findings in symptomatic patients				Main clinical presentation		
type of porphyria	**enzyme defect**	**enzyme activity (%)**	**inheritance pattern**	**urine**	**stool**	**erythrocyte**	**plasma peak (nm)**	**acute attacks**	**skin fragility, blisters**	**acute painful photosensitivity**
AIP	HMBS	50	AD	PBG > ALA, Uro I	normal	normal	615–620	yes	no	no
VP	PPOX	50	AD	PBG, ALA, Copro III	Proto > Copro III	normal	624–627	yes	yes	no
HCP	CPOX	50	AD	PBG, ALA, Copro III	Copro III, ratio isomer III/I > 2.0	normal	615–620	yes	yes	no
ADP	ALAD	1–5	AR	ALA, Copro III	normal	Zn Proto	none	yes	no	no
PCT	UROD	50	AD in 25%	Uro I + III, Hepta	Hepta, Isocopro	normal	615–620	no	yes	no
EPP	FECH	10–35	AD/AR	normal	Proto	Free Proto	626–634	no	no	yes
CEP	UROIIIS	2–30	AR	Uro I, Copro I	Copro I	Zn and Free Proto	615–620	no	yes	no

AIP – acute intermittent porphyria; VP – variegate porphyria; HCP – hereditary corpoporphyria; ADP-ALA dehydratase deficiency porphyria; PCT – porphyria *cutanea tarda*; EPP – erythropoietic protoporphyria; CEP – congenital erythropoietic porphyria; HMBS – hydroxymethylbilane synthase; PPOX – protoporphyrinogen oxidase; CPOX – coproporphyrinogen oxidase; ALAD – ALA dehydratase; UROD – uroporphyrinogen decarboxylase; FECH – ferrochelatase; UROIIIS – uroporphyrinogen III synthase; AD – autosomal dominant; AR – autosomal recessive; PBG – porphobilinogen; ALA – δ-aminolevulinic acid, Uro I or III – uroporphyrin isomer I or III; Copro I or III – coprporhyrin isomer I or III; Hepta – heptacarboxylic porphyrin; Isocopro – isocoproporphyrin; Proto – protoporphyrin; Zn and Free Proto – zinc and free protoporphyrin; nm – nanometer.

of iron in protoporphyrin IX. The enzyme deficiency is caused by mutations in the *FECH* gene which is located on chromosome 18q21.3. To date, 190 mutations responsible for EPP have been described [13, 19, 31].

In almost 95% of cases the disease is inherited in an autosomal dominant fashion with low clinical penetration. In about 4% of cases it is autosomal recessive. There is also the X-linked form of EPP (so called X-linked dominant EPP) due to mutations in *ALAS2* gene and acquired EPP associated with myelodysplastic disorder [31].

Clinical expression in autosomal dominant variant of EPP is related to the coinheritance of *FECH* gene mutation and low-expression of *IVS3-48C* allele in trans to each other. *IVS3-48C* allele is reported in approximately 10% of healthy European population [30, 32].

FECH deficiency leads to the over-accumulation of free protoporphyrin in erythrocytes, reticulocytes, erythroblasts, liver, plasma and skin. Excessive accumulation of protoporphyrin in erythrocytes and skin result in painful skin lesions following sun exposure (painful oedema, swelling, erythema and scary lesions). Hydrophobic protoporphyrin forms crystals in hepatocytes and bile canaliculi which slow down hepatic bile flow. Cholelithiasis due to gallstones containing protoporphyrin is reported in about 25% of EPP patients. Liver failure affects 2–5% of patients; many present iron deficiency with microcytic anemia and low vitamin D levels [1, 13, 31].

The main biochemical abnormality observed in symptomatic EPP patients is massive increase of protoporphyrin in red cells. Feacal protoporphyrin is also higher. Urinary heme precursors and porphyrins are within normal value. Plasma porphyrin fluorescence shows a characteristic peak at 634 nm (Table 1). FECH activity is reduced to 10–35% of the normal value for symptomatic patients. In asymptomatic carriers FECH deficiency is about 50% [1, 31].

Congenital Erythropoietic Porphyria (CEP, Günter Disease)

CEP results from almost complete deficiency of UROIIIS (EC 4.2.1.75) which catalyses the conversion of linear tetrapyrrole hydroxymetylbilane to cyclic tetrapyrrole uroporphyrinogen III. The enzymatic defect is due to mutation in *UROIIIS* gene and is inherited in an autosomal recessive fashion [33, 34].

The *UROIIIS* gene is located on chromosome 10q25.2-q26.3. Up to date 49 mutations responsible for CEP have been described [19].

UROIIIS deficiency results in overproduction and accumulation of uroporphyrin I and coproporphyrin I isomers which are non-physiological and pathogenic. Characteristic for CEP is severe photosensitivity manifested as skin and soft tissues lesions on the sun-exposed areas (blisters, hypo- and hyperpigmentation, scars and disfigurement usually on hands, nose, cheeks, ears and eyelids). Soft tissue atrophy and ocular disorders may appear. In ultraviolet light teeth appear brownish, discolored and fluorescent. Hemolytic anemia and splenomegaly are reported as well as signs of hemolysis, morphological changes in red blood cells, leucopenia and thrombocytopenia, increased levels of bilirubin, deficiency of iron-binding capacity. Excessive amounts of porphyrins tend to accumulate in various tissues, particularly bones leading to osteolisis, osteoporosis and bone deformation. The disease manifests quite early, soon after birth. In CEP affected infants red fluorescent nappies are a good diagnostic marker. No differences in CEP clinical symptoms in men and in women have been observed. The average life span for most patients is 40–60 years [1, 16, 30, 33].

In CEP patients urinary uroporphyrin I and coproporphyrin I as well as faecal coproporphyrin I excretion are markedly increased. Urinary ALA and PBG excretion is normal (Table 1) [1, 30, 33].

Diagnosis of Porphyria

Diagnostic testing in porphyria-suspected symptomatic patients is based on determination of urinary heme precursors (PBG and ALA) and urinary, faecal, erythrocyte and plasma porphyrins. Excessive amounts of these biochemical markers confirm the diagnosis and their characteristic profile in different biological specimens indicates the specific type of porphyria (Table 1). Enzyme activity measurement and genetic testing confirm the type of porphyria and help to identify the asymptomatic – but at-risk-family members of the index patient. DNA analysis which identifies a family specific, causative mutation is now the method of choice for family studies, especially in non-erythroid variant of AIP and in cases when low-normal and high-reduced values of enzyme activity overlap or hematological diseases responsible for abnormal blood cells distribution coexist to present a false normal or abnormal enzyme activity [1, 9, 35–37].

Polymerase chain reaction (PCR) and direct sequencing of the analyzed exons and their flanking regions is the most common mutation analysis usually sufficient to detect missense, nonsense, frameshift and splice mutations. For detection of large intragenic deletions/duplications the multiplex ligation-dependent probe amplification (MLPA) or gene dosage analysis by fluorescent PCR are recommended [36, 38]. Sensitivity for mutation detection in *HMBS*, *CPOX* and *PPOX* genes is 97–100%. [39].

In conclusion, porphyrias are a diverse group of uncommon metabolic disorders caused by inherited deficiencies of the enzymes involved in the heme biosynthesis. Mutations of the genes of these hemasynthetic reactions have been identified. Porphyria *cutanea tarda* (PCT) is an exception, in which the enzyme deficiency is in most cases acquired. Each defective enzyme results in a characteristic clinical phenotype of porphyria. In any patient with a long history of undiagnosed abdominal pain or/and atypical neuropsychatric syndromes porphyria should be considered in differential diagnosis.

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