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Clinical Symptoms, Laboratory Findings and Diagnosis of Porphyria Diseases

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Introduction

Porphyrias are diseases caused by the defect(s) in the heme biosynthetic pathway. Porphyria should be considered as a differential if a patient is present with abdominal pain and/or neurovisceral syndromes caused by accumulation of heme precursor(s). While porphyrins are normally detected in small amounts in healthy individuals, these compounds are excreted in large quantities in the urine, feces, blood and plasma in patients with hereditary and acquired porphyrias. The acquired factors include alcohol, smoking, hepatitis C, estrogens, Human Immunodeficiency Virus (HIV) infection). This is due to inborn errors in heme biosynthesis and in hemolytic anemia, resulting from increased heme biosynthesis. There are at least nine different porphyrias which include: Acute Intermittent Porphyria (AIP), Hereditary Coproporphyria (HCP), Variegate Porphyria (VP), delta-aminolaevulinic Acid Dehydratase Deficiency Porphyria (ADP), Porphyria Cutanea Tarda (PCT), Hepatoerythropoietic Porphyria (HEP), Congenital Erythropoietic Porphyria (CEP), Erythropoietic Protoporphyria (EPP), and X-Linked Protoporphyria (XLP). The group of erythropoietic protoporphyrias are cutaneous types which include EPP, XLP, CEP and HEP [1,2].

The heme biosynthetic pathway involves the conversion of the substrate's glycine and succinyl coenzyme A to heme which consists of four enzymes present in the cytosol and four enzymes present in the mitochondria. The heme inhibits the hepatic ALA synthase 1 in the rate-limiting step. The ALA dehydratase enzyme catalyzes the conversion of ALA to Porphobilinogen (PBG). Hydroxymethylbilane is formed by the conversion of PBG by Porphobilinogen Deaminase (PBGD). The uroporphyrinogen converts hydroxymethylbilane to uroporphyrinogen III. The Uroporphyrinogen Decarboxylase (UROD) enzyme converts uroporphyrinogen III to coproporphyrinogen III which undergoes oxidation to protoporphyrinogen IX. The ferrochelatase enzyme converts protoporphyrinogen IX to heme in the presence of iron [3-6]. The number of intermediates is dependent on endogenous and exogenous stressors by the induction of 5-Aminolevulinate Synthase enzymes (ALAS-1 and ALAS-2), which catalyze the first step in heme biosynthesis [7].

Each type of porphyria has a unique pattern of accumulation and is associated with characteristic clinical features. The porphyrin precursors, ALA and PBG, injure neurons and the porphyrins cause damages to the skin [8]. The acute porphyrias present with neurovisceral symptoms, whereas cutaneous porphyrias present with blistering of the skin. The porphyrias are classified as acute if patients present with neurovisceral acute attacks and as cutaneous if they present with blistering or photosensitivity of the skin. Also classified as hepatic or erythropoietic depending on the major site of expression of enzyme deficiency and presence of excessive amounts of heme precursors [3]. The selective blockage at specific enzymatic steps results in the excessive amounts of heme intermediates such as ALA, PBG and uro-, copro-, or protoporphyrins.

In symptomatic patients, the diagnostic tests include identification and quantification of urinary heme precursors (PBG and ALA) and urinary, fecal, erythrocyte and plasma porphyrins. The presence of large amounts of these specific biochemical markers confirms the diagnosis and establish the specific type of porphyria. Measurement of specific enzyme activity and establishing the genetic profile further confirm the type of porphyria and also help to identify the asymptomatic family members of the patient.

Diagnosis of the porphyrias is usually made by clinical history in association with increased amounts of porphyrins or porphyrin precursors in the urine, feces, and blood [9-13]. Diagnosis is also essential to enable specific treatments to be started as soon as possible. Screening of family

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Table 1: Hepatic and erythropoetic human porphyrias as inheritance pattern.

Type of Porphyria	Inheritance Pattern	Affected Enzyme	Principal Clinical Features	Tissue Site	Principal Site of initial accumulation	Blistering Skin Lesions	Enzyme Activity (%)
AIP	Autosomal dominant	Porphobilinogen Deaminase (PBGD)	Acute neurovisceral	Hepatic	Liver	Never	50
HCP	Autosomal dominant	Coproporphyrinogen Oxidase (CPOX)	Acute neurovisceral, rarely blistering, Cutaneous	Hepatic	Liver	Rarely	50
VP	Autosomal dominant	Protoporphyrinogen Oxidase (PPOX)	Acute neurovisceral, commonly blistering, Cutaneous	Hepatic	Liver	Commonly	50
ADP	Autosomal recessive	Delta-Aminolaevulinic Acid Dehydratase (ALAD)	Acute neurovisceral	Hepatic	Liver	Rarely	1-5
PCT type 1	Acquired	Uroporphyrinogen decarboxylase (UROD)	Cutaneous, blistering	Hepatic	Liver	Frequently	50
PCT Type 2	Autosomal dominant	UROD	Cutaneous, blistering	Hepatic	Liver	Frequently	50
HEP	Autosomal recessive	UROD	Cutaneous, blistering	Hepatic	Liver	Frequently	2-30
CEP	Autosomal recessive	Uroporphyrinogen III Synthase (UROS)	Cutaneous, blistering	Erythropoietic	Erythroblast	Frequently	2-30
EPP - Classical Form	Autosomal dominant	Ferrochelatase (FECH)	Cutaneous, skin lesions	Erythropoietic	Erythroblast	Frequently	10-35
EPP - Variant Form	Sex-linked recessive	Delta-Aminolaevulinic Acid Synthase erythroid-specific form (ALAS2)	Cutaneous, skin lesions	Erythropoietic	Erythroblast	Frequently	10-35
XLP	Sex-linked recessive	ALA synthase, erythroid specific form ALAS2	Cutaneous, skin lesions	Erythropoietic	Erythroblast	Infrequently	10-35

members is essential to decrease the risk of acute porphyrias and counselling about avoidance of potential precipitants [2]. When porphyrias are suspected, simple first-line tests can be used to establish the diagnosis in all symptomatic patients. This review describes pathogenesis, clinical features, clinical findings, diagnosis, clinical testing/workup, laboratory findings, affected populations, and related disorders. Table 1 describes hepatic and erythropoietic human porphyrias as inheritance pattern. The biochemical findings in urine, stool, erythrocytes and plasma for both acute and cutaneous porphyrias are summarized in Table 2.

Acute Porphyrias

Acute porphyrias are a heterogeneous group of rare, inherited metabolic diseases that result from a catalytic defect in 1 of 4 enzymes involved in heme biosynthetic pathway and typically present as an acute attack with neurovisceral symptoms [4,14]. The term of Acute Hepatic Porphyria (AHP) is used for four disorders that can present as an acute attack of pain and other neurological symptoms**:** AIP, HCP, VP, and the extremely rare ADP [2,15,16]. The acute porphyrias VP and HCP can also present with light-sensitive skin fragility and blisters [2,15].

The pathogenesis of neurovisceral symptoms in acute porphyrias have not been fully elucidated. The deficiency of heme can affect neuronal function or the precursor or ALA and PBG may have direct neurotoxic effects [3-5].

The three most common acute porphyrias are AIP, HCP and VP, which are autosomal dominant disorders that present with identical attacks of neurological symptoms after puberty and more commonly in females than males. Acute attacks can cause increases in PBG in all these three porphyrias. AIP is the second most common porphyria in humans and the most common of the three acute porphyrias. Photosensitivity of the skin can occur in HCP and VP. Skin lesions do not occur in AIP except with concurrent severe renal insufficiency [17]. Blistering skin lesions are common in VP and less common in HCP. ADP is very rare and less understood, with only six documented male patients [18], including a child with severe manifestations [19].

Porphyrias can be classified by: Mode of inheritance (autosomal dominant or autosomal recessive), site of overproduction of heme precursors (liver or erythrocytes) and clinical presentation (acute neurovascular attacks or cutaneous findings). The latent porphyria - refers to patients who have a mutation but have not yet had an acute attack. Acute porphyria attacks can occur in all of these conditions. Patients may present with acute life-threatening attacks due to certain type of medications, hormonal changes, starvation, and other factors. Acute porphyria attacks typically consist of severe abdominal pain, nausea, constipation, confusion, and seizure, and can be life-threatening [2,15,16].

Pathophysiology

Porphyrias are either hepatic or erythropoietic forms depending on the site of the major enzyme deficiency which are inherited as either Autosomal Dominant (AD), Autosomal Recessive (AR), or less commonly as X- linked [14]. Liver is the site of the four (AIP, HCP, VP, and ADP) acute porphyrias and also to PCT (one of the cutaneous porphyrias). The AIP is an autosomal dominant acute hepatic porphyria. The enzyme affected is Porphobilinogen (PBG) Deaminase also referred to as Hydroxymethylbilane Synthase (*HMBS*) [4,5,14].

The HCP and VP are also autosomal dominant inherited porphyrias and both present with cutaneous manifestations. The AIP, VP, and HCP have a 50% of respective deficiencies show low penetrance; 90% of heterozygotes are asymptomatic for life. ALAD porphyria, the rarest acute porphyria, which is caused by a defect in the ALA dehydratase enzyme, has an autosomal recessive inheritance

Table 2: Biochemical Laboratory Findings in Urine, Stool, Erythrocytes and Plasma.

Type of Porphyria	Biochemical Laboratory Findings			
	Urine	Stool	Erythrocytes	Plasma
AIP	PBG > ALA, Uroporphyrin, Coproporphyrin.	Porphyrin levels normal or occasional slight increase in Coproporphyrin and Protoporphyrin. Total porphyrins may be increased due to presence of Uroporphyrin.	Porphyrin levels normal. Decreased PBGD activity by approximately 50% (most cases).	ALA and PBG levels increased. Plasma fluorescence emission peak maximum near 618-622 nm.
HCP	PBG > ALA. Coproporphyrin III increased.	Coproporphyrin III markedly increased.	Porphyrin levels are normal or slightly increased.	Porphyrin levels are normal. Plasma fluorescence emission peak maximum near 618-622 nm.
VP	PBG > ALA. Coproporphyrin III increased.	Protoporphyrin IX > Coproporphyrin III.	Porphyrin levels are normal or slightly increased.	Porphyrin-peptide conjugate. Plasma fluorescence emission peak maximum near 626-628 nm.
ADP	PBG normal. ALA and coproporphyrin III increased.	Porphyrin levels normal or slightly increased.	Zinc protoporphyrin level markedly increased. ALAD activity markedly decreased.	ALA, Porphyrin levels normal or slightly increased. Plasma fluorescence emission peak maximum near 618-622 nm.
PCT	ALA and PBG are normal. Uroporphyrin (I & III) and Heptacarboxyl porphyrin increased. Slight increase in copro-, penta- and hexa- carboxyl porphyrins.	Penta-, Heptacarboxyl porphyrins and high levels of Isocoproporphyrin are present.	Porphyrin levels normal. Zinc protoporphyrin normal or mildly elevated.	Uroporphyrin and Heptacarboxyl porphyrin increased. Plasma fluorescence emission peak maximum near 618-620 nm.
HEP	ALA and PBG levels are normal. Increased levels of Uroporphyrin, Hepta-, Hexa-, Pentacarboxyl, and Coproporphyrin levels are present.	Penta-, Heptacarboxyl porphyrins and Isocoproporphyrin levels are increased.	Zinc protoporphyrin markedly elevated.	Uroporphyrin and Heptacarboxyl porphyrin levels increased. Plasma fluorescence emission peak maximum near 618-620 nm.
CEP	ALA and PBG are normal. Uroporphyrin I and Coproporphyrin I levels increased.	Coproporphyrin I increased.	Zinc protoporphyrin, Uroporphyrin I, Coproporphyrin I, and Protoporphyrin levels are increased.	Uroporphyrin I and Coproporphyrin I levels increased. Plasma fluorescence emission peak maximum near 618-620 nm.
EPP	ALA and PBG are normal. Porphyrins (especially coproporphyrin) increase only with hepatopathy.	Protoporphyrin and total porphyrin levels normal or slightly increased.	Metal-free protoporphyrin, Zinc protoporphyrin < 15% of total in classic EPP patients. Protoporphyrin level increased.	Protoporphyrin level increased. Plasma fluorescence emission peak maximum near 632-636 nm.
XLP	Porphyrins (especially Coproporphyrin) increase only with hepatopathy.	Protoporphyrin IX and total porphyrin levels normal or slightly increased.	Metal-free protoporphyrin, Zinc protoporphyrin 15 to 50% of total in XLP patients. Protoporphyrin level increased.	Significantly increased production of ALA, accumulating as protoporphyrin IX in erythroblasts. Plasma fluorescence emission peak maximum near 632-636 nm.

pattern [3-5].

Acute Intermittent Porphyria (AIP)

Pathogenesis: AIP is caused by partial deficiency of PBGD with low clinical penetration. AIP is an autosomal dominant disorder caused by mutations in the *HMBS* gene with 50% deficiency of *HMBS* (EC 4.3.1.8) which catalyzes the condensation of four PBG molecules to hydroxymethylbilane [15]. The 10 kb *HMBS* gene is located on 11q24.1-q24.2 chromosome and consists of 15 exons, 39 bp to 438 bp long. There are two promotors located in the 5' flanking region and intron 1 of *HMBS* gene. Two types of exons 1 and 3-15, and 2-15 are generated. These two transcripts initiate erythroid-nonspecific and erythroid-specific isozymes of *HMBS,* respectively. In most patients, HMBS deficiency occurs both in erythroid and non-erythroid cells (so called classical AIP). In 5% of non-erythroid AIP patients, *HMBS* activity is normal in erythrocytes but reduced in other tissues. Both types of AIP have the same clinical manifestations [20].

The *HMBS* gene mutations responsible for AIP are mostly mutations that affect both HMBS isozymes (classical AIP). The mutations within exon and intron are affected only as an erythroid-nonspecific enzyme variant (non-erythroid AIP). Most of them are point mutations with R1 98W identified in northern Sweden [20-22] (Cardiff; www.hgmd.cf.ac.uk). In 90% of patients with mutation, porphyria symptoms never develop and excrete normal levels of urinary ALA and PBG. About 10% of patients become symptomatic.

Causes: In majority of people with a mutation in *HMBS* without symptoms, additional factors ("triggers") are required to cause symptomatic acute porphyria. The susceptibility to specific triggers may vary during a patient's lifetime. These triggers alone can stimulate increased heme synthesis in the liver or in combination with certain endocrine factors, certain drugs, alcohol consumption, caloric restriction, stress, or infections. Combination of genetic and environmental factors are necessary for developing symptoms of AIP. Mutations in the *HMBS* gene can lead to PBGD deficiency, which in turn lead to the accumulation and release of ALA and PBG from the liver.

Clinical features: Clinical features can be associated with a range of symptoms and physical findings that can potentially involve multiple organ systems of the body and severity is variable from person to person. The AIP episodes develop over the course of several hours or a few days and the individuals usually recover within days. The recovery can take much longer if not diagnosed and treated.

The AIP attacks occur mostly in women in 20s or 30s of age. Because of the menstrual cycle, the AIP attacks occur in 3 to 5% of affected women more than four times per year for a period of many years. Symptoms include severe abdominal pain and also pain in the neck, lower back, buttocks, arms and legs. Neurological symptoms such as peripheral neuropathy, numbness or tingling or burning sensations in the feet and arms, and muscle weakness in the legs causing motor paralysis can occur. Some individuals can develop psychological symptoms such as: Anxiety, depression, disorientation, and altered consciousness. Hyponatremia may develop rapidly causing the onset of seizures. In individuals with chronic AIP, kidney

failure and liver cancers such as Hepatocellular Carcinoma (HCC) or Cholangiocarcinoma (CC) can develop.

The suggested theories for the underlying pathogenesis of AIP include: a) the porphyrin precursor such as ALA is a neurotoxin that damages nerve tissue; and b) heme deficiency in nerve cells (neurons) contributing to the development of symptoms. More research is necessary to determine the exact underlying mechanisms.

Clinical findings: The most common initial symptom is the severe abdominal pain.

- Extremity pain, nausea, vomiting, constipation or diarrhea, abdominal distention, ileus, and urinary retention are frequently present.
- Symptoms usually occur as neuropathic attacks lasting for days or weeks.
- Seizures and mental symptoms can develop.
- Sympathetic over reactivity symptoms such as tremors, tachycardia, sweating, hypertension can develop.
- Attacks may be precipitated by: progesterone, reduced caloric or carbohydrate intake, infection, or surgery.
- In chronic AIP patients, there is an increased risk of hepatocellular carcinoma.

Diagnosis: AIP symptoms are accompanied by increased production and excretion of ALA and PBG. However, some individuals without AIP symptoms can have elevated porphyrin precursors. A diagnosis is based on identification of symptoms from patient history, clinical evaluation and certain specialized tests. AIP should be suspected in individuals with repeated episodes of abdominal pain with muscle weakness, hyponatremia and psychological and neurological symptoms.

Clinical testing and workup: During acute AIP attacks, urinary PBG and ALA excretion is high with PBG predominant. Urine porphyrins are also intense with dark red or brown color containing high levels of uroporphyrins. Fecal porphyrins are normal or slightly elevated. Urinary amounts of ALA and PBG remain increased during remission. The HMBS activity in erythrocytes returns to normal [2,16,23,24].

If urinary PBG excretion is increased, additional testing of fecal and blood porphyrin measurements are essential to distinguish AIP from VP or HCP. These tests can be performed with a random (spot) urine sample protected from light.

Laboratory findings:

- In fecal samples, porphyrin levels are normal or occasional slight increase in coproporphyrin and protoporphyrin.
- Porphyrin levels are normal in erythrocytes.
- Acute attacks are accompanied by increased production and excretion of PBG.
- Rapid screening for a substantial increase in urinary PBG is recommended.
- Concentrations of ALA and PBG in urine are typically ALA=25 to 100 mg/day and PBG=50 mg/day to 200 mg/day during attacks.
- In fecal samples, porphyrin levels are normal or occasional slight increase in coproporphyrin and protoporphyrin.
- Porphyrin levels are normal in erythrocytes.
- Decreased PBG deaminase activity, approximately 50% of normal value occurs in 90% of cases.
- Molecular genetic testing is usually not essential to confirm a diagnosis as the porphyrin biochemical findings are characteristic of AIP.
- However, molecular genetic testing to detect a mutation in the HMBS gene is usually required so that family members can be offered testing for this mutation.

Affected populations: In Europe, the prevalence of symptomatic AIP is reported to be 5.9 per million people in the general population. Due to founder effect, prevalence is higher in Sweden. AIP can occur in individuals of all ethnic backgrounds, although it may be less frequently reported in African-Americans. Women are affected by AIP more often than men and most common in young or middle-aged women.

Related disorders: The acute attacks that characterize AIP are similar to those seen in three other forms of porphyria, specifically HCP, VP and ADP. Other diseases such as: Guillain-Barre Syndrome (GBS), tyrosinemia type-I and lead metal (Pb) poisoning can also cause symptoms that mimic acute porphyria.

The GBS is a rare autoimmune disorder with inflammation of the nerves (polyneuritis) causing muscle weakness and sometimes complete paralysis.

The Tyrosinemia type-I is a rare disorder caused by the failure to properly breakdown tyrosine which leads to abnormal accumulation of tyrosine, its metabolites and ALA in the liver, kidneys and central nervous system resulting in severe liver disease. Tyrosinemia type I can progress to cirrhosis and Hepatocellular Carcinoma if left untreated. Untreated children can also suffer neurological crises.

The lead metal (Pb) toxicity causes acute abdominal pain, constipation and neuropathy. Lead metal inhibits several of the enzymes of heme biosynthesis, which can result in an increase in urine coproporphyrin and ALA excretion, but not PBG excretion. It can also cause an increase in erythrocyte protoporphyrin concentration, although this is all zinc-protoporphyrin. The blood-lead measurement is the definitive test for lead metal poisoning.

Hereditary Coproporphyria (HCP)

Introduction: The HCP is inherited as an autosomal dominant trait and characterized by 50% deficiency of Coproporphyrinogen Oxidase (CPOX) enzyme deficiency. This results in the accumulation of porphyrin precursors and caused by a mutation in the CPOX (EC 1.3.3.3) gene. HCP can cause life-threatening complications if undiagnosed.

Pathogenesis: The CPOX (EC 1.3.3.3) gene is responsible for conversion of coproporphyrinogen III to protoporphyrinogen IX. Mutations in the CPOX gene can lead to deficient activity of CPO enzyme in the body which can lead to insufficient heme production and to the accumulation of CPO precursors in the liver. More research is needed to determine the specific underlying mechanisms.

HCP is mostly latent before puberty as in other acute porphyrias

[25,26]. The gene locus encoding CPOX has been assigned to chromosome 3q12 and contains 7 exons. To date, 65 *CPOX* gene mutations have been described [22]. Eighty percent of HCP patients present acute attacks similar to those in other acute hepatic porhyrias. Like in VP, about 30% of HCP patients also present skin lesions. Skin lesions are the only clinical manifestation in 5% of HCP patients [2]. During HCP attack, the main urinary and fecal biochemical abnormality is the markedly increased coproporphyrin, especially isomer III. PBG, ALA, and uroporphyrin values in urine are also increased. During remission, the urinary and fecal values may be normal [2,23,27].

Causes: The CPOX gene mutation can be inherited from either parent, or can be the result of a new mutation (gene change) in the affected individual. There is 50% risk of passing the CPOX gene from mother to child in each pregnancy regardless of the sex of the resulting child. Factors such as: hormonal changes, use of certain drugs, excess alcohol consumption, infections, and dietary changes are also required to trigger the appearance of HCP symptoms.

Clinical features: The HCP attacks usually develop over the course of several hours or a few days. If an acute attack is not diagnosed and treated promptly, recovery can take much longer. The HCP attacks occurs in the 20s and 30s of age. Attacks are more common in women than men. Pain is not localized to one area of the body. Pain in the abdomen and the lower back occur chronically. Some patients may develop muscle weakness in the feet, legs, all extremities and the body trunk (motor paralysis) and the respiratory muscles. Abdominal pain can be associated with nausea, vomiting, constipation. In a minority of cases, pain primarily affects the back and the arms and legs. Hyponatremia may occur during an attack which can lead to the onset of seizures. Affected individuals may also experience tachycardia, hypertension, cardiac arrhythmias, orthostatic hypotension, seizures and peripheral neuropathy. Peripheral neuropathy is characterized by numbness or tingling and burning sensations in arms and legs can occur. Some patients may develop psychological and psychiatric symptoms including irritability, hallucinations, paranoia, disorientation, mental confusion, psychosis, delirium, depression, anxiety, and insomnia. Some affected individuals may develop skin (cutaneous) lesions affecting the sun-exposed areas of skin such as the hands and face leading to severe pain, burning, and itching (photosensitivity). The skin may become fragile and develop fluid-filled blisters (bullae).

Clinical findings:

- Clinical features of HCP manifest when there is partial (~50%-heterozygous) or nearly complete (homozygous) deficiency of the CPOX enzyme.
- Attacks are initiated by the same factors similar to as in AIP.
- Neurovisceral manifestations are less severe than in AIP.
- Cutaneous features are seen in ~30% of patients. These include vesiculobullous eruption, resembling that in PCT or HEP, usually involving the face, hands or other sun-exposed skin areas.
- The skin lesions resembling PCT occurs much less commonly than in VP.
- Increased risk for Hepatocellular Carcinoma.

Diagnosis: The diagnosis of HCP should be considered if there is elevation of urinary ALA and PBG. However, unlike AIP, ALA excretion often exceeds that of PBG, and these levels usually normalize more quickly between attacks. Elevation of fecal coproporphyrin III alone without elevation of protoporphyrin IX differentiates HCP from VP. The fecal and urinary coproporphyrin III levels typically increase 10 to 200-times the normal levels. Diagnosis is usually confirmed by identifying the CPOX mutation.

Clinical testing and workup: Screening tests can help diagnose HCP by measuring the levels of certain porphyrin precursors, PBG and ALA in the urine. Acute attacks are always accompanied by markedly increased excretion of PBG. If urinary PBG is sufficiently increased in a spot urine test, then a qualitative 24-h urine analysis for both PBG and ALA should be performed and compared to urine sample results from when the individual did not exhibit symptoms. During recovery phase, PBG and ALA may return to normal levels. Patients may have elevated levels of coproporphyrin in the urine, but this finding is nonspecific.

Specific tests are necessary to exclude HCP from VP or AIP. Fecal coproporphyrin analysis can reveal markedly increased levels of coproporphyrin in stool samples, which is characteristic of HCP. Molecular genetic testing positive for CPOX mutation can confirm the diagnosis.

Patients and family members should be counseled on information about HCP, causes of HCP attacks, how to check the safety of prescribed medication(s), details of patient support groups, and membership in the American Porphyria Foundation.

Laboratory findings:

- During acute attacks of HCP, PBG, ALA and Uroporphyrin levels in urine are increased.
- Some patients may have high concentrations of coproporphyrin III isomer, but this finding is nonspecific.
- Markedly increased levels of fecal porphyrins with a predominance of coproporphyrin III isomer is characteristic of HCP.
- During remission, the urinary and fecal values may become normal [2,23,27].
- Detection of CPOX mutations will confirm the diagnosis of HCP.

Affected populations: HCP affect males and females in equal numbers, with more prevalent symptoms in females. The incidence and prevalence of HCP is unknown.

Management: Treatments for acute attacks of HCP are similar to AIP.

Related disorders: Three other forms of porphyria, specifically VP, AIP and ADP may develop acute attacks that characterize HCP. The cutaneous symptoms of HCP can resemble those seen in VP and PCT (Rare Disease Database 2020). Polyneuritis (inflammation of the nerves) can mimic the autoimmune GBS. HCP should be differentiated from GBS for prompt treatment of HCP and the avoidance of some specific medications which worsen an acute attack.

Variegate Porphyria (VP)

Introduction: Variegate Porphyria (VP) is both an acute porphyria and a cutaneous porphyria. Each child of an individual with VP has a 50% chance of inheriting the pathogenic variant; while offspring

who inherit the variant may or may not develop manifestations, most do not. Prenatal testing for pregnancies at increased risk for VP is possible if the pathogenic variant in an affected family member has been identified.

Pathogenesis: VP is an autosomal disorder caused by a heterozygous deficiency of Protoporphyrinogen Oxidase (*PPOX*) activity with variable penetrance. The gene has been localized to chromosome 1q22. It is predominantly a cutaneous disease (60%) with blistering lesions on Sun-exposed areas of the skin, but an appreciable proportion of patients (40%) also have neuro-visceral symptoms, as seen in acute porphyrias. The blistering is caused by accumulation of uroporphyrin and coproporphyrin, which are toxic.

VP is characterized by approximately 50% deficiency of PPOX (EC 1.3.3.4) which oxidizes protoporphyrinogen IX to protoporphyrin IX. The 8 kb *PPOX* gene encoding PPOX has been assigned to chromosome 1q22 and consists of 13 exons. To date 177 variations in *PPOX* gene mutations have been described. Among them most common are missense and frameshift mutations [Rare Disease Database 2020] [28,29]. VP mutations also show high heterogeneity with the exception of founder effect mutations, e.g. mutation R5 9W in South Africa [22,30]. VP is both an acute and a cutaneous and porphyria. Each child of an individual with VP has a 50% chance of inheriting the pathogenic variant; while offspring who inherit the variant may or may not develop manifestations, most do not.

Causes: VP is an autosomal dominant disorder. This means that a male or female carrying the gene will pass it on to half of his or her children. In most people with VP signs and symptoms may only become apparent when they are exposed to non-genetic factors such as stress, dieting or fasting, and certain hormones. The combinations of increased demand and reduced activity of *PPOX* disrupt heme production and triggers an acute VP attack.

Clinical features: Most VP patients are asymptomatic. Bullae, erosions and ulcers may develop at an early age after minimal trauma to light-exposed skin. Other chronic skin findings include milia, scarring, thickening, and areas of skin pigmentation. Hyperpigmentation and hypertrichosis may occur in the face. In dark-skinned individuals living in cold places, cutaneous manifestations usually improve in winter.

Symptoms can occur after puberty. Acute neurovisceral attacks occur especially in women of child-bearing age. Acute manifestations are highly variable and may become chronic. Symptoms are more common in women than men and the most common manifestations include: abdominal pain; constipation, pain in the back, chest, and extremities, anxiety; seizures, and psychiatric disturbances. Acute attacks may be severe and fatal.

Clinical findings: About 20% of VP patients may also present only cutaneous photosensitivity with 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 [2].

VP patients present with acute neurovisceral attack (± skin lesions). The neurovisceral symptoms in VP and other acute porphyrias are likely related to accumulation of a heme pathway intermediate such as ALA [31,32]. Increases in ALA and Porphobilinogen (PBG) may result from inhibition of hepatic Porphobilinogen Deaminase (PBGD) by protoporphyrinogen IX and coproporphyrinogen III, which accumulate in the liver in VP [33]. Elevation of Coproporphyrin III may be explained by the close association of PPO with Coproporphyrinogen Oxidase (CPO) in the mitochondrial membrane [34].

Cutaneous manifestations include:

- Chronic blistering photosensitivity, most commonly on the backs of the hands.
- Chronic features include blisters, milia, scarring, thickening, and skin pigmentation.
- Skin lesions resemble to those of PCT and other blistering cutaneous porphyrias.

Neurovisceral symptoms most commonly include the following:

- Abdominal pain is typically severe, steady rather than cramping, and diffuse.
- The pain is neuropathic rather than inflammatory.
- Ileus and bladder distension may be present.
- Constipation
- Pain in the back, chest, and extremities
- Anxiety
- Seizures
- Muscle weakness due to motor neuropathy.
- Hyponatremia, which increases the risk for seizures.

Diagnosis of VP: The diagnosis of VP is made from the results of blood, urine and stool tests. Patients with biochemically active VP will have increased PBG in a spot urine sample and/or increased plasma porphyrins, with distinctive fluorescence peak at approximately 626 nm to 628 nm at neutral pH. The latter is of much help in differential diagnosis, although it is not observed in all subjects. Increased fecal porphyrins with a predominance of both coproporphyrin III and protoporphyrin IX are observed in stool samples. The diagnosis of VP should be confirmed by demonstrating a genetic mutation in PPOX or decreased PPOX activity in cells, such as lymphocytes. The diagnosis of VP is made by finding excess coproporphyrin in urine and both coproporphyrin and protoporphyrin in feces. The most sensitive screening test for VP is probably a plasma porphyrin assay [35].

If PBGD activity is normal, VP should be considered in the differential diagnosis. The differentiation of VP from HCP is usually possible following fecal porphyrin analysis. The observation of urinary 8- and 7-carboxylic porphyrins and isocoproporphyrin in PCT is usually sufficient for differentiation of PCT from VP in patients with cutaneous manifestations.

Screening of family members is best achieved by measuring fecal porphyrin concentrations. Fecal porphyrins may not be elevated in pubertal or elderly heterozygotes. Prenatal testing for pregnancies at increased risk for VP is possible if the pathogenic variant in an affected family member has been identified.

Clinical testing and workup: The significant biochemical finding in VP is the elevated fecal porphyrin excretion. Clinical VP symptoms include markedly increased fecal protoporphyrin and coproporphyrin with predominant protoporphyrin concentration. Urinary PBG, ALA and porphyrins are also increased, especially coproporphyrin.

The urinary PBG, ALA and uroporphyrin may be normal during remission, whereas fecal protoporphyrin and coproporphyrin levels remain elevated.

The PPOX oxidizes protoporphyrinogen to protoporphyrin. As a result of decreased activity of PPO, protoporphyrinogen accumulates within hepatocytes and is mostly auto-oxidized to protoporphyrin before excretion in the bile and feces. Cutaneous manifestations of VP are associated with elevations of plasma porphyrins, indicating that excess porphyrins are transported in plasma from the liver to the skin.

Laboratory findings: Clinical VP symptoms include markedly increased fecal 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 fecal protoporphyrin and coproporphyrin levels remain elevated. Specific for VP is plasma fluorescence. An increased plasma porphyrin fluorescence emission peak at 626 nm to 628 nm differentiates VP from all other porphyrias, except EPP [2,23,35,36].

- Urinary PBG excretion is usually normal, or only borderline increased.
- ALA excretion is in most patients increased to a lesser extent than PBG.
- Measurement of total urinary porphyrins is also recommended, since porphyrin elevations persist longer in VP than do elevations in ALA and PBG, keeping in mind that urinary porphyrin elevations are much less specific than elevations in PBG [12,31,35].
- VP is readily differentiated from AIP and HCP by biochemical testing [12,31]. Fractionation of urinary porphyrins is usually not informative, since uroporphyrin and PBG are often concurrently elevated in AIP, HCP or VP, although coproporphyrin increases may be especially prominent in VP and HCP. Plasma and fecal porphyrin determinations are most useful in distinguishing these conditions.
- VP is characterized by increased fecal porphyrin and also coproporphyrin. Fecal porphyrins are increased, with a predominance of both coproporphyrin III and protoporphyrin IX. In HCP, plasma porphyrins are usually not increased (and skin lesions are relatively uncommon), and fecal porphyrins are markedly elevated with a predominance of coproporphyrin III that is distinctive.
- Fecal coproporphyrin concentrations may be increased, in combination with a coproporphyrin III:I ratio greater than 2.0. Fecal protoporphyrin concentrations are usually at least 2-fold greater than coproporphyrin. However, protoporphyrin is less fluorescent than coproporphyrin, thus HPLC peaks of similar sizes are usually observed. Calculation of relative response factors of each porphyrin using standards is therefore obligated for quantitation.
- As with AIP and HCP, chronic mild increases in liver function tests, especially transaminases, may be seen in patients with persistent elevations of ALA, PBG, and porphyrins.
- When urine PBG is elevated, plasma fluorescence scanning with a fluorescence peak at ~626 nm to 628 nm can establish or exclude VP since this characteristic peak is not found in any other type of porphyria.

Enzymatic and DNA testing for VP: Assay of PPO activity in cells that have mitochondria, such as fibroblasts and lymphocytes, are useful for confirming a diagnosis of VP but are not widely available [37]. This provides further diagnostic confirmation and enables other family members who are carriers of the same mutation and at risk for the disease to be reliably identified. In most countries, each VP family will likely have a different mutation, whereas in South Africa almost all VP patients have the highly prevalent R59W missense mutation [30]. Plasma fluorescence scanning and measurement of PPO activity are useful for detecting family members who have inherited VP, but are less sensitive than DNA studies [12,38]. Mutation analysis is not appropriate for initial diagnosis of VP in either acutely ill patients or those with chronic skin lesions.

Treatment: Treatment and management of acute attacks of VP is similar to management of other acute hepatic porphyrias. The avoidance of precipitating drugs such as barbiturates and contraceptive steroids are crucial for the management of VP.

Photosensitivity can be minimized by protective clothing and a beta-carotene analogue (Canthaxanthin) can to be helpful. Patients with cutaneous manifestations should limit sun exposure, wear protective clothing and use sunscreens that block long-wave lengths ultraviolet and blue light. Antibiotics should be used to treat skin infections. Topical steroids should be avoided.

Phlebotomy or low-dose hydroxychloroquine (an antimalarial drug) therapy are not effective to treat VP. The prognosis for VP seems to be good although it has a life-threatening potential after ingestion of precipitating drugs [35,39].

ALA Dehydratase Deficiency Porphyria (ADP, Doss porphyria)

Introduction: 5-Aminolevulinic Acid Dehydratase Deficient Porphyria (ALADP or ADP): Only less than ten cases have been diagnosed so far. This condition was first recognized by Doss et al. [40,41]. The symptoms are similar to that seen in AIP. ALAD activity is inhibited by many chemicals or compounds, such as lead metal or succinylacetone. Clinical ADP symptoms resemble those characteristics which are connected to other acute hepatic porphyrias but present no photosensitivity or skin lesions [23,42,43].

Pathogenesis: ADP is an autosomal recessive disorder which results from severe deficiency of ALAD enzyme (EC 4.2.1.2.4) which catalyses the condensation of two molecules of ALA to form one molecule of PBG. ADP usually manifests in childhood in homozygotes with ALAD activity between 1% to 5% of normal value. A 50% decrease of ALAD is observed in asymptomatic heterozygotes. Clinical symptoms manifest if there is a profound (>90%) deficiency of ALAD. 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 [22].

Causes: ADP is caused by mutations in the ALAD gene and inherited as an autosomal recessive disorder, meaning both copies of the ALAD gene have a mutation. Factors such as: hormonal changes, infections, use of certain drugs like steroids, excess alcohol consumption, and dietary changes (dieting) are also required to trigger the appearance of HCP symptoms.

Clinical features: The complete range of clinical manifestations of ADP is not well known, because of the paucity of cases reported so far. The presentations and symptoms resemble very similar to other

acute hepatic porphyrias. It includes neurovisceral symptoms, such as vomiting, abdominal pain, neuropathy and chronic paresis. ADP presents no photosensitivity or skin lesions [23,42,43].

Diagnosis: In symptomatic patients, supporting evidence for the diagnosis of ADP includes 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 erythrocytes may also be higher [23]. Diagnosis is established by documenting ALAD deficiency in red blood cells and eliminating other potential causes (lead metal toxicity and tyrosinemia type I). Definitive diagnosis is dependent on the demonstration of defective ALA dehydratase activity and deficiency of enzyme protein in erythrocytes. In three of the documented cases, this activity was approximately 2% of normal values, consistent with a homozygous deficiency. Intermediate decreases in the patients' relatives and in the family presumably reflect the heterozygous deficiency state [44].

The differential diagnosis of ADP includes the other hepatic porphyrias (AIP, HCP and VP) and toxic states in which ALAD activity is suppressed. ADP is characterized by markedly increased production of ALA, such that ALA production is 10 to 20 times that of PBG. On the other hand, AIP is characterized by increased production of both ALA and PBG, often in equimolar amounts. The fact that AIP and ADP are clinically indistinguishable suggests that ALA or its metabolites, rather than PBG, may be the neurotoxic agent. This point is further supported by the finding that patients with hereditary tyrosinemia frequently develop ADP along with its neurologic abnormalities [45], most likely via the marked inhibition of ALAD by succinylacetone [46,47].

Clinical testing and workup: ADP can be differentiated from AIP and the other acute hepatic porphyrias by the following: a) inheritance is autosomal recessive, rather than autosomal dominant; b) production of PBG is not increased, since ALAD is required for PBG synthesis; and c) ALAD activity is markedly reduced to less than 5% of normal. Thus, when neurovisceral symptoms suggestive of a hepatic porphyria are present, urinary ALA, PBG, and porphyrin concentrations should be determined in an aliquot from a 24-h urine collection. In ADP, the excretion of ALA is markedly increased, while excretion of PBG is normal or slightly increased. Normal excretion of ALA is less than 7 mg per 24 h; in an attack of ADP, urinary ALA excretion is markedly elevated, with typical values being 3 to 10 or more times the upper limit of normal. Normal excretion of PBG is less than 2 mg per 24 h [31]. In ADP, normal to slightly increased excretion of PBG is seen. The increase in excretion of PBG in ADP is always significantly less than that of ALA.

Urinary and erythrocyte porphyrins may be elevated in ADP in a nonspecific pattern. Fecal porphyrin excretion is generally within the normal range. The diagnosis is confirmed further by showing marked reduction of ALAD enzyme activity. If ADP is suspected, erythrocyte or lymphocyte ALAD activity should be determined. Activity should be less than 5% of normal in the patient and approximately 50% in both parents [31].

Laboratory findings:

- Increased urinary ALA excretion, greatly in excess of PBG excretion.
- Coproporphyrin III excretion is usually greater than 250 nmol/mmol.
- ALAD activity decreased by more than 80%.
- ALA and coproporphyrin concentrations are at least 8 times the upper limits of normal.
- PBG excretion may be normal or increased up to 5-fold.
- Zinc protoporphyrin in erythrocyte is markedly increased.
- Fecal porphyrin concentration is normal or slightly elevated.

Related disorders: ALAD activity is inhibited by many chemicals or compounds, such as lead metal or succinylacetone.

Management: Treatment for acute attacks in ADP patients is similar to management of other acute hepatic porphyrias. Withdrawal and avoidance of drugs and precipitating factors known to be harmful in other acute porphyrias is recommended.

Cutaneous Porphyrias

Introduction

The cutaneous porphyrias are inherited or acquired enzyme defects in the porphyrin-heme biosynthetic pathway, resulting in production of phototoxic porphyrins in the liver or bone marrow. Cutaneous porphyrias include: CEP, PCT (type 1), EPP, and XLP. The XLP is an erythropoietic form of porphyria and clinically similar to EPP. As mentioned in the previous section, Acute Porphyrias, HCP and VP also have cutaneous manifestations in the skin.

Acquired PCT is the most common cutaneous porphyria in most parts of the world, which is caused usually due to chronic liver disease and liver iron overload. EPP, the next most common cutaneous porphyria, is an inherited disorder which leads to the accumulation of bile-excreted protoporphyrin causing gallstones and, rarely, liver disease. Cutaneous porphyrias cause symptoms involving cutaneous photosensitivity.

An overview of cutaneous porphyrias

- Cutaneous porphyrias are a diverse group of conditions, all showing skin diseases due to a problem in the heme biosynthetic pathway.
- The visible light (not ultraviolet) that is relevant for the skin manifestations.
- Also associated with complicating diseases in organs other than the skin.

Porphyria Cutanea Tarda (PCT)

Introduction: PCT is a chronic form of hepatic porphyrias and classified as "acquired or sporadic" or "familial" based on the absence or presence of a *UROD* mutation. Familial cases may present at an earlier age, but in these cases the family history is often negative for PCT. Finding a *UROD* mutation warrants genetic counseling.

PCT type 1 (acquired or sporadic) - Absence of a *UROD* mutation; accounts for approximately 75% of cases, mostly men [21,48]. Patients with type 1 PCT have normal erythrocyte enzyme activity with no *UROD* gene mutations.

PCT type 2 (familial) - An autosomal dominant with heritance of a *UROD* mutation affecting one allele (i.e., heterozygous defect); present in approximately 25% of cases. Inheritance is autosomal dominant with low penetrance, so there are often no relatives with PCT. Patients with type 2 PCT have *UROD* gene mutations as well as decreased *UROD* activity in liver and erythrocytes. Other factors must be present to reduce *UROD* from 50% of normal (due to the

mutation) to <20% of normal and cause significant porphyrin accumulation and clinical features [1,49].

PCT type 3 (familial) - Apparent familial inheritance without a *UROD* mutation; may be due to other inherited factors (e.g., *HFE* mutations) or shared acquired factors

Pathogenesis: PCT is the most frequent cutaneous porphyria due to partial deficiency of *UROD* (EC 4.1.1.37), which decarboxylates *uroporphyrinogen III* to *coproporphyrinogen III*. *UROD* gene is located on chromosome 1p34 and consists of 10 exons [50]. To date 121 *UROD* gene mutations responsible for hereditary PCT have been described [22].

Causes: Excessive alcohol intake, HCV, HBV and HIV infections, HFE mutations, estrogens, hemochromatosis, and inherited uroporphyrinogen decarboxylase deficiency are some of the risk factors. These usually lead to hepatic iron overload, the main PCT causative factor [1,2,49,51].

Clinical features: Characteristic PCT symptoms are skin lesions on sun-exposed areas (hands, neck and face) in the form of blisters with fluid, erosions, scars and hyperpigmentation. The skin is coarse. PCT patients can develop cirrhosis and Hepatocellular Carcinoma [2,23]. PCT patients usually have markedly higher levels of urinary, fecal and plasma porphyrins, especially urinary uroporphyrin and heptacarboxylate porphyrin as well as fecal heptacarboxylate porphyrin and isocoproporphyrin. Urinary PBG is normal; ALA is normal or slightly increased.

In PCT remission, urinary, plasma and fecal porphyrins return to normal. The hepatic *UROD* activities are reduced to about 25% of normal value in symptomatic types 1 and 2 PCT patients. In type 1 PCT, erythrocyte *UROD* activity is normal and reduced by about 50% in type 2 with either symptomatic or asymptomatic [1,2,23].

Diagnosis: PCT causes blistering skin lesions as the predominant clinical manifestation; neurovisceral attacks do not occur. PCT is caused by acquired inhibition of hepatic *UROD* to less than approximately 20% of normal, which occurs in the presence of iron and a variable combination of acquired factors (e.g., alcohol, smoking, hepatitis C, estrogens, HIV infection). Genetic factors are present in some patients; these may include heterozygosity for a *UROD* mutation, which predisposes to the disease by reducing *UROD* activity to 50% of normal in all tissues from birth, and *HFE* (hemochromatosis) mutations (homozygous or heterozygous), which increase iron absorption.

Individuals who are heterozygous for a *UROD* mutation but do not manifest clinical findings of PCT are referred to as asymptomatic carriers. Some may have subclinical elevations of plasma and urinary porphyrins.

Clinical testing and workup: Urinary ALA may be modestly increased, but PBG excretion is normal. Plasma porphyrin measurement is the preferred screening test which can differentiate PCT from VP. Highly carboxylated porphyrins are increased in patients with PCT, especially in liver, plasma, and urine. The uroporphyrin and heptacarboxyl porphyrin usually exceed hexa- and pentacarboxyl porphyrins. The presence of predominately uroporphyrin and 7-carboxylate porphyrin in urine and elevated stool isocoporphyrin/ coproporphyrin ratio is almost diagnostic of PCT.

The presence of urinary uroporphyrin more than coproporphyrin favors PCT, whereas, urinary coproporphyrin greater than uroporphyrin favors VP or HCP. The inherited deficiency of UROD is present in 20% of PCT patients and can be demonstrated by measuring the enzyme in red blood cells [39,52].

Some salient features of PCT include:

- **Iron and *HFE* pathogenic variants.** Mild-to-moderate iron overload is typically found in persons with Familial PCT; some degree of hepatic siderosis is seen in almost all affected individuals.
- **Alcohol.** PCT has long been associated with excessive alcohol use.
- **Smoking and cytochrome P450 enzymes.** Smoking is commonly associated with alcohol use in PCT [51].
- **Hepatitis C.** Reported prevalence of hepatitis C in individuals with PCT has ranged from 21% to 92% in various countries; it is seen more frequently in type 1 PCT than in Familial PCT.
- **Estrogens.** Estrogen use is a common susceptibility factor in women with PCT [51] and also presents a risk for men (e.g., those taking estrogen for treatment of prostatic cancer). Discontinuation of oral estrogen use leads to resolution of the symptoms. Use of transdermal estrogens in women has been shown to be safe.
- **Antioxidants.** Substantial reductions in plasma levels of ascorbate and carotenoids have been noted in some individuals with PCT.

Laboratory findings:

- The best preliminary test for PCT diagnosis and differentiation from other skin-symptom porphyrias is the plasma porphyrin fluorescent assay with a characteristic emission peak approximately at 620 nm.
- Predominance of uro- and hepta-porphyrins in urine.
- Hepta-, penta- and isocoproporphyrins in feces.
- During remission, PCT patients will have normal porphyrin levels in urine, feces and plasma.

Affected populations: Worldwide most patients (~80%) have a sporadic form of PCT where the UROD gene is normal. Genetic family screening can be carried out in the ~20% of cases where PCT is inherited. Hepatoerythropoietic Porphyria (HEP) is a rare form of PCT where UROD gene mutations are present on both alleles.

Related disorders: The pseudoporphyria patients have skin manifestations that can clinically and histologically imitate PCT. Chemicals such as the pesticide hexachlorobenzene can induce a porphyria that caused an epidemic of a porphyria, with cutaneous features similar to PCT, in Turkey [53].

Management: Management of PCT consists of visible-light photoprotection and treatments to reduce serum iron while awaiting the effects of treating the underlying cause of liver disease (if possible).

Hepatoerythropoietic Porphyria (HEP)

Introduction: HEP is a cutaneous porphyria which causes blistering skin lesions as the predominant clinical manifestation without neurovisceral attacks [50].

Pathogenesis: HEP is due to UROD deficiency in all tissues

which leads to the accumulation of uroporphyrinogen and other intermediate products of the reaction in cells with a high demand for heme production which include the erythron and the hepatocyte. The oxidized porphyrins (mostly uroporphyrin and heptacarboxylporphyrin) are then transported into the plasma and eventually into the urine. These excess porphyrins are deposited in the skin and other tissues causing blisters.

HEP is inherited as an autosomal recessive trait. When a patient inherits the same abnormal gene for the same trait from each parent, recessive genetic disorders occur. The patient will be a carrier for the disease, if he/she receives one normal gene and one abnormal gene for the disease.

Causes: HEP is caused by severely deficient *UROD* activity due to the mutation in both *UROD* alleles (homozygous and compound heterozygous mutations). The *UROD* enzyme activity is usually less than 10% of its normal levels and symptoms develop due to abnormal accumulation of porphyrins and related chemicals in the body, especially in the bone marrow, red blood cells, liver and skin. When porphyrins accumulate in the skin, they absorb sunlight and enter an excited state (photoactivation) which results in the characteristic damage to the skin. The liver removes porphyrins from the blood plasma and secretes into the bile.

Clinical features: Clinical manifestations of HEP include extreme photosensitivity, fluid-filled blisters, hypertrichosis, and scarring over the affected skin areas. Repeated sun exposure can lead to scleroderma-like changes [54]. There may be a red/brown discoloration of teeth due to the deposition of porphyrins in the enamel layer of the developing tooth. Symptoms of HEP start during childhood, with similar frequency in females and males. Signs and symptoms generally resemble those of CEP. HEP is a rare form of PCT where *UROD* gene mutations are present in both alleles. Symptoms and clinical features of PCT and HEP are indistinguishable. No increased risk for Hepatocellular Carcinoma has been identified in persons with HEP.

Diagnosis: The diagnosis of HEP is established when porphyrins are elevated in the urine (predominantly uroporphyrin and heptacarboxylporphyrin) with significantly increased erythrocyte zinc protoporphyrin. The diagnosis of HEP should be further confirmed by molecular studies that demonstrate mutations affecting both *UROD* alleles. Identification of biallelic pathogenic variants in *UROD* confirms the diagnosis. These features of HEP generally resemble those of CEP.

Clinical testing and workup: The biochemical laboratory findings in HEP resemble those that are observed in PCT and include predominant excretion of uroporphyrin, heptacarboxylate porphyrin and isocoproporphyrins. Porphyrin precursors, ALA and PBG, are normal. In contrast to PCT, porphyrins are increased in bone marrow and red blood cells as well as liver, plasma, urine and feces. Marked elevation in erythrocyte protoporphyrin is characteristic of HEP. Erythrocyte porphyrins are predominantly type III isomers [55-57].

HEP is differentiated from CEP by the patterns of individual porphyrins in plasma, urine, and erythrocytes, and by a marked reduction in erythrocyte *UROD* activity and erythrocyte *UROD* activity is more reduced than in Familial type 2 PCT [23,55,58].

Laboratory findings:

- Hepatic *UROD* enzyme activity is approximately 15% to 20% of normal.
- The *UROD* protein level is determined by genotype (e.g., ~50% in individuals with a null allele and a partial loss-of-function allele).
- Significant elevation in erythrocyte protoporphyrin is characteristic of HEP.
- Erythrocyte porphyrins are predominantly type III isomers.
- Erythrocyte zinc protoporphyrin levels are significantly increased.
- Plasma porphyrins are increased. Fluorescence emission peaks (at neutral pH) at approximately 620 nm following excitation with light of approximately 400 nm to 410 nm (Soret band) [59].
- In urine, there is a predominance of uroporphyrin and hepta-, hexa- and pentacarboxyl porphyrins. Coproporphyrin levels are also increased.
- In urine, ALA and PBG levels are normal or minimally increased.
- In stool, levels of fecal isocoproporphyrin and hepta- and pentacarboxyl porphyrins are increased.

Related disorders: The susceptibility factors shown to modulate the phenotype of familial PCT are important in HEP [60]. The genetic and environmental susceptibility factors may reflect their frequency in the general population, e.g., Hepatitis C. The frequency and the degree to which these risk factors are involved in type I PCT (sporadic) and familial PCT also differ in HEP [61,62].

Treatment: HEP is treated the same way as CEP. Unlike Familial PCT, phlebotomy and chloroquine are not effective in HEP [56,63]. Protecting against exposure to sunlight (including the long-wave UV light) is the most important treatment. Older individuals should avoid known precipitating factors: alcohol, oral estrogen, smoking, and drugs that induce the cytochrome P450s.

Genetic counseling: Identification of *UROD* mutations in a previous case in a family can enable genetic counseling. Once the *UROD* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis for HEP are possible. Those family members with biallelic *UROD* pathogenic variants can be counseled regarding sun protection and avoidance of known susceptibility factors.

Erythropoietic porphyrias

The Erythropoietic Porphyrias (CEP and EPP) usually manifest cutaneous photosensitivity in early childhood but in rare cases they develop later in adult life.

Congenital Erythropoietic Porphyria (CEP, Gunter Disease)

Introduction: CEP is the most severe of the cutaneous porphyrias and least common. The prevalence is less than one per million in the United Kingdom.

Pathogenesis: CEP is an autosomal recessive disorder with homo- or heteroallelic mutations in the *UROS* gene or rarely, the X-linked *GATA1* gene [64]. The enzymatic defect is due to mutation in *UROIIIS* gene and is inherited in an autosomal recessive fashion. CEP results from almost complete deficiency of *UROIIIS* (EC 4.2.1.75). This gene

catalyses the conversion of linear tetrapyrrole hydroxymethylbilane to cyclic tetrapyrrole *uroporphyrinogen III* [65,66]. The *UROIIIS* gene is located on chromosome 10q25.2-q26.3. Approximately 49 mutations responsible for CEP have been described [22]. *UROIIIS* deficiency leads to excessive accumulation of uroporphyrin I and coproporphyrin I isomers which are pathogenic.

Recessive genetic disorders occur when an individual inherits two copies of an abnormal gene for the same trait, one from each parent. If an individual receives one normal gene and one gene for the disease, the person will be a carrier for the disease, and usually will not show symptoms. The risk for two carrier parents to both pass the defective gene and have an affected child is 25% with each pregnancy. The risk to have a child who is a carrier like the parents is 50% with each pregnancy. The chance for a child to receive normal genes from both parents and be genetically normal for that particular trait is 25%. The risk is the same for males and females.

Causes: Mutations in the *UROS* gene cause CEP. Due to impaired function of *UROS* enzyme, excessive levels of the specific porphyrins accumulate in tissues of the body which lead to the clinical symptoms of CEP.

Clinical features: Characteristic features 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, and deficiency of iron-binding capacity.

Diagnosis of CEP: For the diagnosis of CEP, characterization of porphyrin patterns to confirm a deficiency of uroporphyrinogen III cosynthase and to determine the nature of the underlying mutation are indicated. Some patients reported to have CEP might have had PCT or HEP [67,68]. With improved diagnostic testing and molecular methods, these diseases are now readily differentiated.

Genetic analysis may be useful in CEP patients where prenatal diagnosis may be requested due to the serious clinical complications of this disorder. If heterozygous parents have a child with this disease, CEP can be detected *in utero* in future pregnancies by performing one or more of the following tests: a) red-brown discoloration and increased porphyrins (especially uroporphyrin I) in amniotic fluid [69]; b) measurement of UROS activity in cultured amniotic fluid cells [70]; and c) direct detection of UROS gene mutations in cultured amniotic cells [71].

Clinical testing and workup: The disease manifests quite early, soon after birth. In CEP affected infants, red fluorescent nappies are a good diagnostic marker. There is no difference in the CEP clinical symptoms in men or women have been observed. The average life span for most patients is 40 to 60 years [1,2,23,65].

In CEP patients, urinary uroporphyrin I and coproporphyrin I as well as fecal coproporphyrin I excretion are markedly increased. Urinary ALA and PBG excretion is normal [1,2,65]. Urinary porphyrin excretion is markedly increased [up to 50 to 100 mg/day, normal range: than 0.2 mg per 24 h and consists mostly of uroporphyrin I, heptacarboxylporphyrin, and coproporphyrin III, with lesser increases in hexa- and penta-carboxylporphyrins [72]. Although the absolute excretion of type III isomers may be increased, the predominant increase is in type I isomers, which may represent >95% of the excreted porphyrins. In contrast to other porphyrins, type I isomers of uro- and coproporphyrins represent less than 5% of total urinary porphyrins.

In most reported cases of CEP, circulating erythrocytes have large amounts of uroporphyrin I, and lesser but still excessive amounts of coproporphyrin I. Red cell protoporphyrin may also be increased, and in some reported cases was the predominant porphyrin in erythrocytes, as in the bovine form of this disease. However, other porphyrias, such as HEP and EPP, need to be considered if protoporphyrin is the predominant erythrocyte porphyrin. The elevation of both urinary and erythrocyte uroporphyrin I isomer levels is specific for CEP.

Laboratory findings:

- Urinary uroporphyrin I, coproporphyrin I and fecal coproporphyrin I excretions are markedly elevated.
- Urinary ALA and PBG excretion is normal [1,2,65].
- Fecal coproporphyrin I (80%) accumulate in large amounts due to decarboxylation of uroporphyrin.
- However, isocoproporphyrins are not increased [73].
- Plasma porphyrin fluorescence emission peak approximately at 620 nm is present.
- High levels of uroporphyrinogen I and coproporphyrinogen I are present in urine and erythrocytes.
- DNA testing with mutation analysis of the uroporphyrinogen III synthase gene is performed at porphyria research units in several countries and commercially available now in the United States.

Treatment and management: Management of CEP includes protection from sunlight and UV exposure, meticulous skin care, red cell transfusions for severe anemia, and supportive care (e.g., treatment with hydroxyurea, oral charcoal, or splenectomy). Hematopoietic cell transplantation is the curative option.

Erythropoietic Protoporphyria (EPP)

Introduction: EPP is due to reduced ferrochelatase activity. It is the second most common cutaneous porphyria, affecting approximately 2.3 per 100,000 population in the Dundee area. This estimate is higher than a survey of diagnosed UK cases which suggested 0.86 per 100,000**.** The prevalence estimate of EPP in Slovenia is 1.75 per 100,000 inhabitants [74]. Similar discrepancies were seen in prevalence estimates in Denmark [75]. The EPP is usually manifest cutaneous photosensitivity in early childhood. EPP develops in adult life in rare cases [1,2].

EPP is the most frequent porphyria to present in childhood. Its clinical features are very different from those of the cutaneous porphyrias that present mainly with blistering and fragility. EPP can occur rarely as an acquired problem, usually associated with myelodysplastic conditions such as sideroblastic anemia**.** Within the differential, there are sometimes certain patterns of drug-induced phototoxicity and atypical polymorphic light eruption. Also in the differential, when EPP induces urticaria, it is usually idiopathic solar urticaria. In fact, EPP was originally classified as type VI solar urticaria [76,77].

EPP is inherited in an autosomal dominant fashion in 95% of cases

with low clinical penetration. In about 4% of cases, it is autosomal recessive. In EPP, the FECH deficiency leads to over-accumulation of free protoporphyrin in several tissues: erythrocytes, red blood cells, reticulocytes, erythroblasts, liver, plasma and skin leading to symptoms. In 2% to 5% of patients, liver failure occurs. Many patients with EPP also present iron deficiency with microcytic anemia and low vitamin D levels [2,78,79].

Pathogenesis: EPP results from a partial deficiency of FECH (EC 4.99.1.1.) which catalyses the insertion of iron in protoporphyrin IX. This enzyme deficiency is caused by mutations in the *FECH* gene which is located on chromosome 18q21.3. To date, 90 mutations responsible for EPP have been described [22,78,79].

There is also so-called X-linked dominant EPP due to mutations in *ALAS2* gene and acquired EPP associated with myelodysplastic disorder [79]. In autosomal dominant variant EPP, the clinical expression is related to the coinheritance of *FECH* gene mutation and low-expression of *IVS3-48C* allele in trans to each other. This allele is reported to be present in 10% of healthy European population [1,80].

Causes: EPP is a rare genetic disorder. The classic genetic diseases are the product of the interaction of two genes, one received from the father and one from the mother. It is most common to find that one severe mutation is inherited from one parent and another weak mutation inherited from the other parent. The weak mutation is quite common in normal Caucasians, rare in African Americans and even more common in Japanese and Chinese populations. This mutation is sometime referred to as "hypomorphic" because it results in formation of a less than normal amount of ferrochelatase. But does not cause EPP unless it is paired with a severe mutation. The severe mutation is characteristic for an EPP family and is present in all affected individuals.

Carriers of the severe mutation are not affected because they do not have the weak mutation. Affected individuals and unaffected carriers can transmit the severe mutation to the next generation. Some of their children will have EPP if the other parent has a copy of the weak mutation. Rarely, the weak mutation is absent in an EPP family and two severe mutations are found, with at least one producing some ferrochelatase. The risk of transmitting EPP from affected parent to offspring is 50% for each pregnancy regardless of the sex of the resulting child. The risk is the same for each pregnancy.

Clinical features:

- Excessive accumulation of protoporphyrin in erythrocytes and skin result in painful skin lesions following sun exposure (painful edema, swelling, erythema and scary lesions). Protoporphyrin forms crystals in hepatocytes and bile canaliculi which slow down hepatic bile flow.
- FECH deficiency leads to the over-accumulation of free protoporphyrin in erythrocytes, reticulocytes, erythroblasts, liver, plasma and skin.
- Cholelithiasis due to gallstones containing protoporphyrin is reported in about 25% of EPP patients.
- Fecal protoporphyrin is also higher.
- Urinary heme precursors and porphyrins are within normal value.
- The major clinical symptom is pain in skin when exposed to a few minutes of sunlight (visible radiation) causing redness, purpura and chicken pox-like scarring and a waxy thickening of the skin over the dorsal nose and knuckles. Other features, such as rhagades, can develop [81].
- Palmar keratoderma is especially associated with classic autosomal recessive inheritance [82].

Diagnosis: The diagnosis of EPP is established by measuring an abnormally high level of protoporphyrin in erythrocyte. This increase in protoporphyrin is mostly as free protoporphyrin rather than zinc protoporphyrin. EPP patients have much less zinc protoporphyrin in their erythrocytes than XLP patients. This distinguishes EPP from XLP [52]. During liver failure, the dynamic equilibrium between rates of protoporphyrin production and excretion is altered which leads to increase or decrease of erythrocyte and plasma porphyrin levels and progressively diminishing fecal porphyrin excretion. Abnormal coproporphyrinuria develops when liver function is deteriorating [83-88].

EPP often have anemia with mildly lowered hemoglobin, hematocrit and mean corpuscular volume levels. Monitor serum indices of liver function at 6- to 12-month intervals if baseline values are normal. Abnormal liver function can lead to gallstones, viral hepatitis and other toxic, infectious, immunologic, or metabolic storage disorders [59,88,89]. DNA studies confirm the diagnosis of EPP and essential for genetic counseling since the information about the mutations in patients can be used to guide testing of family members.

- **Laboratory findings:**The major biochemical abnormality observed in symptomatic EPP patients is massive increase of protoporphyrin in red cells.
- Fecal protoporphyrin excretion may be increased, but, in many patients, it remains within the reference range.
- Urinary heme precursors and porphyrins are within normal value.
- Plasma porphyrin fluorescence shows a characteristic peak at 634 nm (Table 2).
- FECH activity is reduced to 10-35% of the normal value in symptomatic patients.
- In asymptomatic carriers, FECH deficiency is about 50% [2,79].
- Protoporphyrin concentration is elevated in red blood cells, plasma and bile.
- The diagnosis is usually made by finding the abnormal levels of protoporphyrin in erythrocytes and plasma.
- Porphyrins are almost always elevated in plasma in EPP, but may be normal in mild cases.
- Urinary porphyrin levels are normal in patients without liver dysfunction.

Treatment and management: In EPP patients, the underlying cause can be resolved only with a bone marrow transplant (which is rarely justifiable in this condition) and hence management consists particularly of visible-light photoprotection and, in some countries, narrowband ultraviolet B phototherapy. Afamelanotide is a promising treatment for EPP and has been approved in Europe since 2014.

X-Linked Protoporphyria (XLP)

Introduction: X-Linked Protoporphyria (XLP) is an extremely rare genetic disorder characterized by an abnormal photosensitivity to sunlight. Symptoms such as severe pain, burning and itching may occur after exposure to the sun, including direct or indirect exposures. Redness, swelling, blistering and severe scarring can occur infrequently.

The XLP was initially described as a variant form of EPP without pathogenic variants of *FECH* and was characterized genetically [90]. XLP affects both males and females. Males usually develop a severe form of the disorder while females with an *ALAS2* mutation may range from having no symptoms (asymptomatic) to developing a severe form of the disorder. The exact incidence or prevalence of XLP is unknown. XLP has only been reported in a handful of families in Europe, South Africa and Japan. XLP comprises up to 10% of those with the protoporphyria genotype [90,91]. The XLP is also called as "Variant EPP".

Pathogenesis: XLP is inherited as an X-linked dominant disorder which is caused by gain-of-function mutations to the *ALAS2* gene located on the X-chromosome. The X-linked dominant disorders are more evident in a female with one normal X-chromosome and one affected X-chromosome. Mutations of the *ALAS2* gene lead to the overproduction of 5-ALAS2 enzyme, which results in the elevation protoporphyrin levels.

Like hemophilia and other X-linked genetic diseases, XLP is more common in men. Women have two X-chromosomes and are usually not affected because they have a normal as well as a mutated *ALAS2* gene. Women with an ALAS2 mutation will pass that mutation to half of their daughters (who will usually be unaffected carriers) and to half of their sons (who will be affected). Men have one X-chromosome only and will be affected if they inherit an ALAS2 mutation.

Causes: XLP is caused by mutations of the ALAS2 gene, which is found on the X-chromosome causing an increase in the production of the enzyme ALAS2 in the bone marrow. Several of these "gain of function" mutations have been described in different XLP families. The symptoms of XLP develop because of the abnormal accumulation of protoporphyrin in the blood, liver, and skin. Abnormal photoactivation of protoporphyrin molecules results in the characteristic damage to the skin. In XLP, protoporphyrin production exceeds that needed for heme and hemoglobin formation.

Clinical features: Hypersensitivity of the skin to sunlight is the characteristic finding of XLP. Some patients experience pain in the right upper area of the abdomen and in the back. Pain is disproportionately severe in relation to the visible skin lesions. The excruciating pain is often resistant to pain medications, even narcotics. Repeated episodes of photosensitivity may eventually cause changes in the skin of affected individuals. Such changes include thickening and hardening of the skin, development of a rough or leathery texture, small facial pock-like pits, and grooving around the lips.

A cholestatic liver disease, referred to as protoporphyric hepatopathy, is a serious complication of XLP. This complication is rare, occurring in fewer than 5% of patients [81,92]. The liver disease can range from mild liver abnormalities to liver failure. Information on liver disease is limited, but the risk of liver disease is believed to be higher in XLP than in EPP. In some EPP patients, the flow of bile through the gallbladder and bile ducts can be interrupted (cholestasis) leading to gallstones by the abnormal accumulation of protoporphyrin [93]. These stones can cause obstruction and inflammation of the gallbladder (cholecystitis). Scarring of the liver (cirrhosis) may also develop and some individuals develop end-stage liver failure. Iron deficiency and mild anemia are common in XLP patients [77].

Diagnosis: The blood tests can detect markedly increased levels of metal-free and zinc-bound protoporphyrin's in erythrocytes. Molecular genetic testing can confirm a diagnosis of XLP by detecting mutations in the *ALAS2* gene.

Clinical testing and workup: Clinical testing and workup is based upon identification of characteristic symptoms, a detailed patient history, a thorough clinical evaluation, and specialized biochemical laboratory tests [94].

Laboratory findings:

- Metal-free protoporphyrin predominates in most XLP patients, suggesting that the capacity of normal FECH activity to insert zinc into protoporphyrin is exceeded.
- A higher ratio of zinc-bound protoporphyrin to metal-free protoporphyrin can differentiate XLP from EPP.
- Plasma total porphyrins are elevated in most patients with XLP and EPP, but less so than in other cutaneous porphyrias, it may be normal in milder cases. Plasma porphyrins are sensitive to light and may degrade rapidly during sample processing [95].
- The fluorescence emission spectrum of plasma porphyrins at neutral pH shows a characteristic emission peak at approximately 634 nm which can distinguish XLP and EPP from other porphyrias (eg, peak near 626 nm in VP, peak near 620 nm in PCT and CEP) [92].
- Protoporphyrin not detectable in urine.
- Protoporphyrin is normal or increased in stool.
- Blood tests to evaluate anemia and iron stores in the body and vitamin D levels, are performed.
- An abdominal sonogram can be done to detect and evaluate liver disease potentially associated with XLP.

Affected populations: The exact incidence or prevalence of XLP is unknown. In studies from the UK, XLP appears to account for about 2% of individuals with the EPP phenotype [96]. In the US, XLP accounts for about 10% of individuals with the EPP phenotype [94]. XLP affects both males and females. Males usually develop a severe form of XLP while females with an *ALAS2* mutation having no symptoms (asymptomatic) to developing a severe form of XLP.

Related disorders: Other conditions that cause signs and symptoms similar to XLP include other cutaneous porphyrias such as EPP, drug-induced photosensitivity, various forms of lupus, and solar urticaria.

Treatment and management: Pediatricians, hematologists, dermatologists, hepatologists, and other healthcare professionals should coordinate plans for an affected child's treatment. Genetic counseling is recommended for affected individuals and their families. Most treatment information is based on EPP, which is clinically similar to XLP.

- Avoidance of sunlight is very beneficial to XLP patients who can include the use of long sleeve clothes made with double layers of fabric or of light-exclusive fabrics, wide brimmed hats, gloves, and sun glasses. Topical sunscreens are generally ineffective. Window tinting and the use of sunscreens in homes and cars are beneficial.

- Avoidance of sunlight can cause vitamin D deficiency and require supplemental vitamin D.

- Beta-carotene (Lumitene) may be given orally to improve tolerance of sunlight.

- Cysteine is also used to improve tolerance to sunlight.

- The drug cholestyramine may be given which absorbs porphyrin.

- Other drug that absorbs porphyrins is activated charcoal.

- Individuals with any form of protoporphyria should avoid substances associated with cholestasis including alcohol and drugs such as estrogens.

- Hepatitis A and B immunizations are recommended.

- Afamelanotide (Scenesse), a controlled-release, long-acting, an alpha-melanocyte-stimulating hormone analogue, increases the production of eumelanin by binding to the melanocriptin-1 receptor in the skin and provides proto-protection by increasing pigmentation and antioxidant properties [97,98]. Afamelanotide showed positive results in the US and Europe. Long-term studies in Europe show good compliance and improved quality of life [99,100].

- Red blood cell transfusions and plasmapheresis have been recommended to treat people with XLP and EPP.

- In individuals with severe liver disease, a liver transplantation may be required.

- Anemia is treated with iron supplementation and carries a risk of increased photosensitivity as in EPP [101].

Conclusions

It is important for physicians to consider the possibility of porphyria when they see patients with symptoms that may be compatible with porphyria disease. The most common presenting symptoms are recurrent episodes of severe abdominal pain, especially occurring in women aged 18 to 45 years, or evidence of acute or chronic photosensitivity.

The porphyrias affecting the skin can be divided into: (1) those that present mainly with visible light–exposed site bullae and fragility (most commonly PCT]), (2) those, particularly EPP, that present with neuropathic-type pain, edema, erythema, and lesions on exposed sites (acute phototoxic porphyria), and (3) the extremely rare, severe, and mutilating porphyrias such as CEP (Günther's disease).

- The single most important test to establish or exclude a diagnosis of an acute porphyria is a rapid test for PBG in the urine. This test should be available and should be run every day of the week, with rapid turn-around times at all major centers, because of the importance of ruling-in or ruling-out the diagnosis of acute porphyria.

- The most important tests when cutaneous porphyria is suspected are plasma and erythrocyte porphyrin levels. If the levels are increased, genetic testing should be performed to establish the specific diagnosis.

- All the porphyrias except AIP and the exceptionally rare ALA dehydratase deficiency porphyria (Doss porphyria) can affect the skin.

- Two of the blistering and fragility porphyrias VP and HCP can also cause acute porphyria attacks.

- Acquired PCT which is not primarily inherited, is a consequence of chronic liver inflammation and liver iron overload.

- EPP can affect the biliary system (rarely the liver) and is associated with anemia.

- The three common cutaneous porphyrias in the UK (Scotland) are PCT (1 in 13,000 people); EPP (1 in 43,000 people); and VP (1 in 240,000 people).

- HCP has skin manifestations identical to those of PCT and VP. The CEP and HEP (homozygous inherited PCT) are usually severe but exceptionally rare (affecting less than one in a million) diseases.

Diagnosis of the Porphyrias

Biochemical laboratory studies are useful for initial screening and proposing differentials. Additional DNA studies confirm the diagnosis of the acute and cutaneous porphyria diseases. Characterization of specific genes, enzymes and mutations causing porphyria disease provide further diagnostic confirmation which enables to reliably identify other family members who are carriers of the same mutation and at risk for the disease. This is essential for genetic counseling since the information about the mutations in patients can be used to guide testing of family members and appropriate treatments.

Acute Porphyrias (Including VP)

Elevations in urinary ALA and PBG are expected during acute attacks of many porphyrias. Such elevations are less marked and more transient in VP (and HCP) than in AIP.

- Urinary PBG and total porphyrins are essential measurements to diagnose acute porphyria attacks. Urine ALA is often measured at the same time as PBG but this is not necessary for initial screening.

- Treatment should be started for symptoms if an acute porphyria is confirmed by substantial elevation of urinary PBG, while further biochemical testing is being performed to determine the type of acute porphyria.

- Total porphyrins and ALA should be measured with the same urine sample if PBG is normal since total porphyrins often remain elevated longer than PBG.

- In ADP, the levels of ALA and total porphyrins (but not PBG) are markedly elevated.

- Plasma or urine porphyrins measurements are the recommended initial test when VP or any other blistering cutaneous porphyria is suspected. If the level is elevated, further testing is done to determine the type of porphyria.

- For VP patients with blistering cutaneous skin lesions, neurovisceral symptoms or both, initial first-line testing should aim to detect all porphyrias that can cause either skin or neurovisceral manifestations.

Cutaneous Porphyrias

- For cutaneous porphyria like PCT, a porphyrin plasma scan along with plasma and urine total porphyrin measurements are appropriate initial tests.
- If plasma and Urine total porphyrins are elevated, then High Performance Liquid Chromatography (HPLC) with fluorescent detection (excitation at 400 nm and emission at 620 nm wavelengths) on urine and stool porphyrins are appropriate to differentiate among PCT, VP, and HCP.
- It is also important to start investigating for underlying cause(s) for iron accumulation, chronic hepatitis B or C, or HIV, if acquired PCT is strongly suspected.
- If EPP or XLP is considered as a differential, then it is appropriate to request a porphyrin plasma scan and quantitative erythrocyte protoporphyrin levels.
- A higher ratio of zinc-bound protoporphyrin to metal-free protoporphyrin will differentiate XLP from EPP.

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