の観察では、変異を有すると考えられる個体の大部分は発症せず、従って浸透率はかなり低く10%程度とされてきた。現在ではなぜ浸透率が低いのかを説明する分子遺伝学的メカニズムが明らかになっており、FECH遺伝子のイントロン3に遺伝子多型IVS3-48T>Cが存在するとスプライシング異常をおこす頻度が高まり、結果としてPTCを生じるため、NMDによってFECH mRNA量が低下することが判明している（Gouya et al., 2002；図2）。つまり、EPPはFECH遺伝子の一方のアリルの酵素活性を明らかに低下させるような遺伝子変異に加え、もう一方のアリルの遺伝子多型IVS3-48Cを併せ持つことによって発症する、すなわち、変異の反対側のアリルのIVS3-48Cが発症を規定している（図3）。FECH遺伝子変異とIVS3-48T/C遺伝子多型との関係を調べた報告によると、ほとんどの症例がIVS3-48CによってEPPの発症が規定されており、本研究班の解析結果も同様であった。従って、EPP家系において、発端者のFECH遺伝子変異が同定されれば、その同胞のうち臨床的に無症状の個体が無症候性キャリアであるかそうでないかが確定できる。EPPの大部分は以上述べた機序による優性遺伝であるが、劣性遺伝の症例がまれに存在する。IVS3-48C多型の頻度には人種差があり、欧米人に比べ日本人ではIVS3-48Cのアリル頻度が4倍高い（Nakano et al., 2006）。従って、本邦ではEPPの浸透率が欧米より高いと考えられる（中野、2009）。

EPPにおける遺伝子診断のもっとも重要な臨床的意義は、潜在的EPP罹患児を発見できることにある。EPPは通常、出生後すぐには発症せず幼児期になって光線過敏を示すようになる。そのため、罹患児と知らずに多量の日光に曝露されると重度の光線過敏症状のみならず、血中に大量に放出されたプロトポルフィリンによる急性肝不全で死に至る危険性がある。従って、EPPと診断された家系では遺伝子診断を行い、特に、光線過敏を示さない幼児において遺伝子型を決定し、発症する可能性の有無を明らかにしておくことが極めて重要である。

その他、EPPの遺伝子診断で問題となる点は2つある。ひとつは肝障害の合併と特異的に関係のあるFECH遺伝子変異が未だ明らかになっていない点である。

これまでのデータから、FECHの活性を著しく低下させるような変異、例えば停止コドンが生じるような変異ではミスセンス変異に比べて肝障害を引き起こす可能性が高いことが示唆されている。しかし、一方ではミスセンス変異であっても肝障害を生じた家系が報告されている。従って、今後さらに症例を増やして、変異の種類と肝障害との関係を分析する必要がある。もうひとつの問題は、一定の割合で変異が検出できない症例が存在する点である。通常のPCRとシークエンスの組み合わせで変異が同定できないEPP症例は、ヨーロッパからの報告では6家系に1つの割合でみられるという（Whatley SD et al., 2007）。こうした症例ではゲノムDNAレベルでのエクソン単位での欠失が生じていることが明らかになっている。我々の検索でも前述のMLPA法を用いたエクソンの定量的解析により、ゲノムレベルでのエクソン欠失を同定し得た症例が存在した（未発表データ）。従って、臨床診断でEPPが強く疑われながらもFECH変異が同定できない症例では、ゲノムレベルでの定量的解析を行う必要がある。

異型ポルフィリン症（variegate porphyria, VP）

VPはEPPについで報告が多い遺伝性皮膚ポルフィリン症であり、常染色体性優性遺伝性である。プロトポルフィリノーゲン酸化酵素をコードするPPOX遺伝子の変異により発症する。本症はその名のとおり、臨床症状が非定形的であり、急性間欠性ポルフィリン症と晩発性皮膚ポルフィリン症（PCT、後述）との混合型と位置付けられている。VPは青壮年期から光線過敏を生じるようになり、しかも自覚症状を欠く場合もあるため、遺伝子変異検索によって初めて診断が確定する症例もまれではない。また、本研究班ではEPPやPCTなど他のポルフィリン症が疑われて検索を進めるうちに、PPOX遺伝子の変異同定をもってVPと診断された症例を4例経験したため、遺伝子診断は極めて有用で

あると言える。

遺伝性コプロポルフィリン症（hereditary coproporphyria, HCP）
HCP はコプロポルフィリノーゲン酸化酵素をコードする CPOX 遺伝子の変異で発症する、常染色体性優性遺伝性のポルフィリン症である。本症のこれまでの報告数は非常に少ないが、やはり他のポルフィリン症との鑑別の過程で遺伝子診断によって診断確定された症例が存在するので、今後報告が増加すると予想される。

先天性ポルフィリン症（congenital porphyria, CEP）
CEP はウロポルフィリノーゲン合成酵素をコードする UROS 遺伝子の変異により発症する、常染色体性劣性遺伝性の非常にまれなポルフィリン症である。本症は出生後間もなく発症するので、臨床診断は困難ではないと思われるが比較的軽症な症例も存在するため、遺伝子診断が決め手となることがある。

晩発性皮膚ポルフィリン症（Porphyria cutanea tarda, PCT）
PCT はポルフィリン症全体の中では最も方向数の多い病型であるが、大多数は後天性と考えられ、遺伝性を示さない。しかし、ウロポルフィリノーゲン脱炭酸酵素をコードする UROD 遺伝子の変異による常染色体性優性遺伝性の症例が報告されているため、遺伝子診断を行う価値はあると考えられる。本遺伝子の変異が両方のアリルに生じると肝性骨髄性ポルフィリン症（hepatoerythropoietic porphyria, HEP）となる。UROD 遺伝子の特定の変異が PCT の発症と関係するとの報告がフランスからなされたが、本邦の PCT では関与が否定されている。しかし、後天性とされる PCT の発症に関する遺伝的背景はいまだに明らかになっておらず、今後の研究が待たれる。

おわりに

本邦における皮膚ポルフィリン症の遺伝子診断は未だ十分なされているとは言えないが、本研究班のこれまでの研究において遺伝子診断により病型確定された症例が数多く経験されたことから、今後も引き続き解析例を増やして診断および治療に有益な情報がもたらされるよう努力したい。

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表1 皮膚ポルフィリン症の病型と原因遺伝子

病型	原因遺伝子産物	遺伝形式
先天性ポルフィリン症	ウロポルフィリノーゲン合成酵素	常劣
骨髄性プロトポルフィリン症	フェロケラターゼ	常優
異型ポルフィリン症	プロトポルフィリノーゲン酸化酵素	常優
遺伝性コプロポルフィリン症	コプロポルフィリノーゲン酸化酵素	常優
晩発性皮膚ポルフィリン症	ウロポルフィリノーゲン脱炭酸酵素	常優
肝性骨髄性ポルフィリン症	ウロポルフィリノーゲン脱炭酸酵素	常劣

常劣、常染色体性劣性遺伝; 常優、常染色体性優性遺伝

図1 イントロン領域に切断点があるエクソン欠失

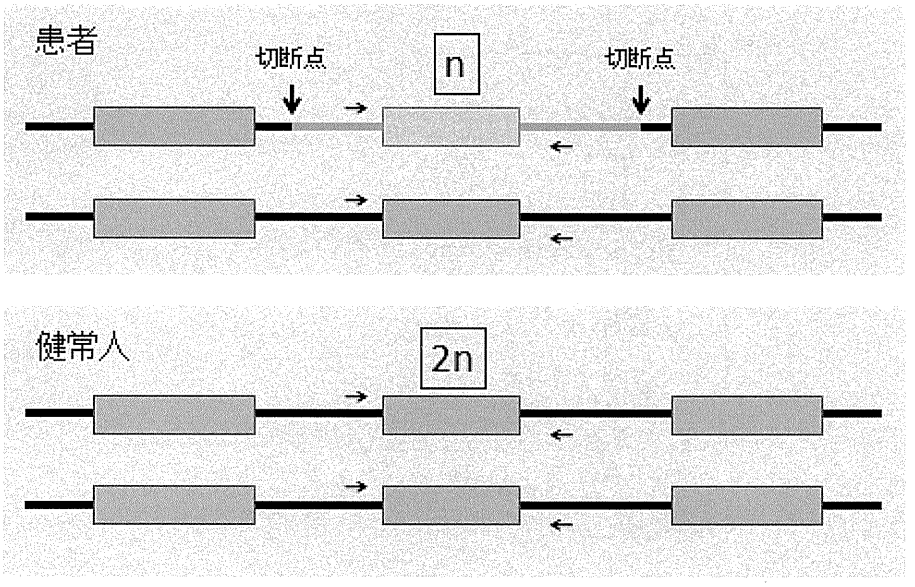


図2　IVS3-48C遺伝子多型とスプライシング異常

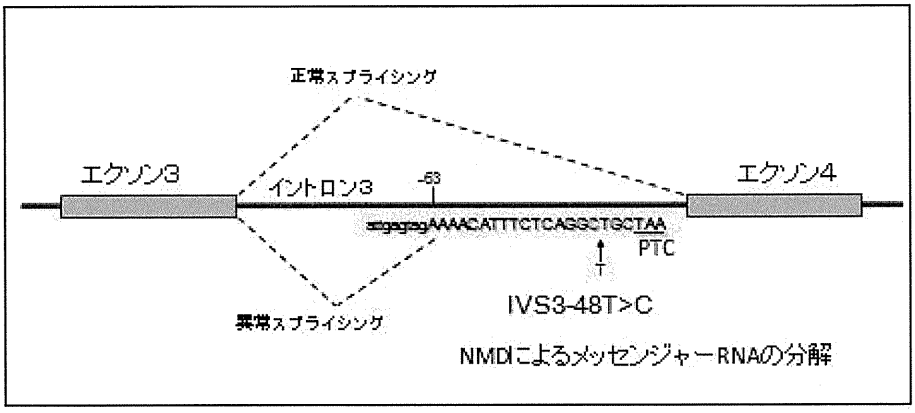
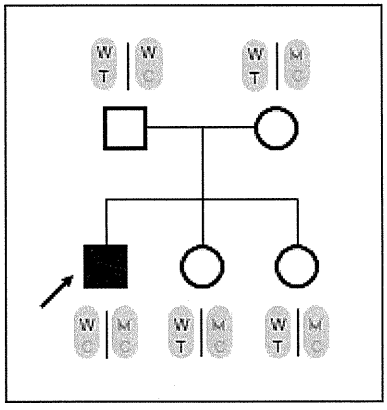


図3　IVS3-48C遺伝子多型で発症が規定されるEPP家系



黒塗り:発症者、矢印:発端者
M: 変異, T: IVS3-48T, C: IVS3-48C,
W: 野生型

Ⅲ. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

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Ⅳ．主な研究成果の刊行物・別冊

2.

Abnormal Porphyrin Metabolism

Masao Kondo

Porphyrias are a group of disorders, which induce excess production of porphyrins, as well as cause their accumulation in the tissues. They also increases the excretion of metabolites, as a result of inherited or acquired deficiencies in the activities of the enzymes of the heme biosynthetic pathway. There are 8 types of porphyria. Like other congenital metabolic disorders, this disorder is very rare, has attracted attention for a long time because of its specific symptoms. Porphyria manifests a wide variety of symptoms, including cutaneous, psychoneurotic, gastrointestinal, and endocrine; endogenous and exogenous environmental factors influence the manifestation of these symptoms. Therefore, acute porphyria may be fatal because of false and/or delayed diagnosis. A poor prognosis may be anticipated. Therefore, it is important that we have accurate knowledge of porphyria. This article reviews on the abnormal porphyrin metabolic disorder.

2.1 Introduction

Heme is synthesized by the cooperative activity of eight enzymes localized in intracellular mitochondria and soluble fractions (Fig. 1).[1,2] It is involved in such processes as detoxification and cellular respiration as a prosthetic group of heme proteins, including hemoglobin and cytochrome P-450. 5-aminolevulinic acid (ALA) synthase (ALAS), the first enzyme in the heme biosynthetic pathway, has two isozymes: erythroid-specific enzyme (ALAS-2 on chromosome X), which is expressed only in erythroid cells, and non-specific enzyme (ALAS-1 on chromosome 3), which is expressed in all organs, including the liver. Regulation of the activities of these isozymes is tissue specific. ALAS-1 is the rate-limiting enzyme in the production of heme in the liver and is controlled via negative-feedback regulation by the intracellular uncommitted heme pool. ALAS-2 is not inhibited by heme.[3,4]

The porphyrias are a group of inherited or acquired metabolic disorders resulting from a deficiency in one of the eight enzymes involved in the biosynthesis of heme. Each enzyme deficiency leads to an increased production and accumulation of porphyrin-related metabolites, and leading to excessive excretion of these metabolites in the urine, plasma, or stool.[5,6]

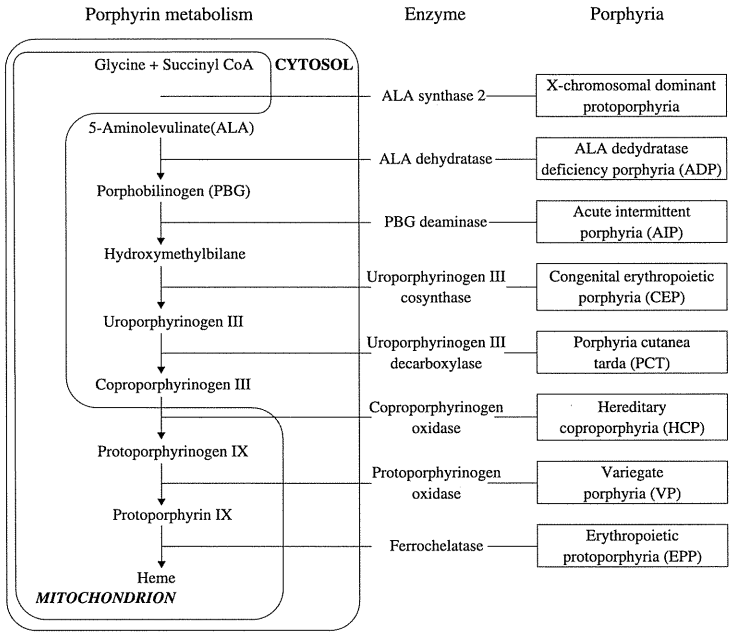

Fig. 1 The pathway of heme biosynthesis and enzymatic deficiencyes leading to specific types of porphyria

2.2 Overview of Porphyrias

2.2.1 Classification

In 1923, the idea that porphyrias resulted from inborn errors of metabolism was proposed by A. E. Garrod.[7] Since then, eight types of porphyria have been discovered.[5,6] Porphyrias occurring in hepatocytes are classified as hepatic porphyrias, and porphyrias occurring in bone marrow erythroblasts are classified as erythropoietic porphyrias. Clinically, porphyrias that cause mainly neurological symptoms are classified as acute porphyrias, whereas those that cause mainly skin photosensitivity are classified as cutaneous porphyrias (Table 1).[8]

2.2.2 Differential Diagnosis

Porphyrias are diagnosed by the detection of porphyrin-related metabolites in the urine, blood, plasma, or stool (Fig. 2). In some cases, diagnosis requires measurement of enzyme activity and gene studies.[9–11]

2.2.3 Pathological Conditions

Cutaneous porphyrias present with various types of skin symptoms due to phototoxicity associated with light exposure.

Table 1 Classification of porphyrias[8)]

Porphyrias			Enzyme defect	Inheritance	Clinical features		Biochemical signs
Classification		Conditon			Skin	Neurologic	Porphyrins and its precursors
Erythropoietic	Cutaneous	Congenital erythropoietic porphyria (CEP)	UROS	Recessive	+++	—	UP I (Urine, Blood)
		Erythropoietic protoporphyria (EPP)	FECH	Dominant	+ – ++	—	FP (Blood)
Hepatic		Hepatoerythropoietic porphyria (HEP)	UROD	Recessive	+++	—	UP III (Urine), ZP (Blood)
		Porhyria cutancea tarda (Familial) (f-PCT)	UROD	Dominant	+ – +++	—	UP III (Urine), isoCP (Feces)
		Porphyria cutanea tarda (Sporadic) (s-PCT)	UROD	Unknown	+ – +++	—	UP III (Urine), isoCP (Feces)
	Acute	Variegate porphyria (VP)	PROX	Dominant	+ – ++	++	ALA, PBG, UP III (Urine), PP, XP (Feces)
		Hereditary coproporphyria (HCP)	CPO	Dominant	— – ++	++	ALA, PBG, CP III (Urine), CP (Feces)
		Acute intermittent porphyria (AIP)	PBGD	Dominant	—	++	ALA, PBG (Urine)
		ALAD deficiency porphyria (ADP)	ALAD	Recessive	—	++	ALA (Urine)

Abbreviations used: UP, uroporphyrin; CP, coproporphyrin; ALA, 5-aminolevulinate; PBG, porphobilinogenn; FP, Free erythrocyte protoporphyrin; ZP, Zinc cherated protoporphyrin; PP, protoporphyrin XI

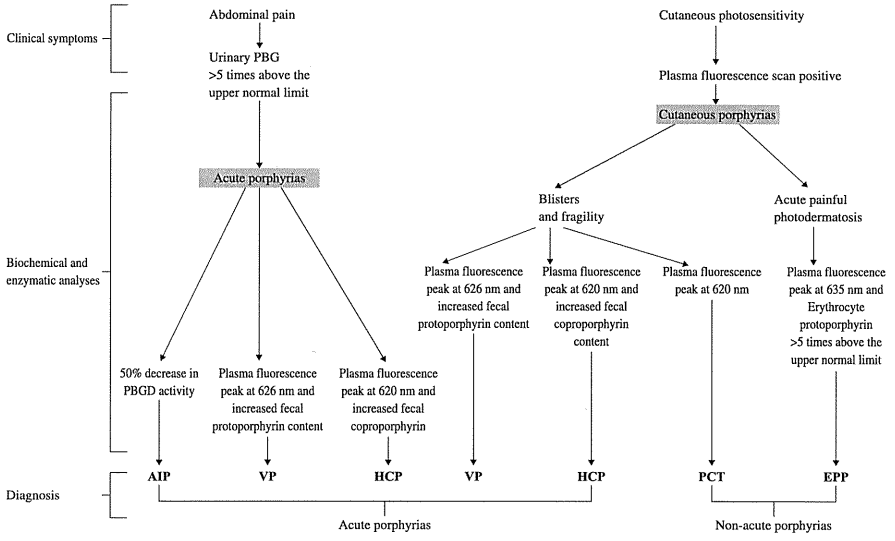

Fig. 2 A flowchart illustrates the diagnostic atrategy for porphyrias (except for rare homozygous forms)[9)]

Acute porphyrias occur commonly in females between adolescence and middle age; factors such as various kinds of drugs; reproductive events, including menstruation and childbearing; contraceptive pill ingestion; infection; starvation; and stress are invariably involved in triggering the development of the disease. The pathological conditions characteristically present with a broad spectrum of symptoms of the neurologic, gastrointestinal, endocrine, and circulatory systems.[12)] Administration of ALA to a patient with abnormal porphyrin metabolism may lead to exacerbations.

2.2.4 Treatment

Acute porphyrias are treated by drip infusion of large amounts of glucose. Concurrently, chlorpromazine is given for pain, painful numbness, and insomnia; pro-

pranolol for hypertension and tachycardia; and diazepam or chloral hydrate for convulsions. Intravenous administration of hematin or heme arginate has been reported to be effective in improving clinical symptoms and abnormal porphyrin metabolism.[13,14] Cimetidine, which suppresses hepatic ALAS activity, has been reported to be efficacious to such an extent that it corrects abnormal metabolism.[15,16]

In cutaneous porphyria, care should be taken to avoid skin injury and exposure to sun light.

2.2.5 Incidence

Acute intermittent porphyria (AIP) is common in Northern Europe (most common in Sweden): the estimated incidence per 100,000 inhabitants is 1. Variegate porphyria (VP) is common in Southern African caucasians: the estimated incidence per 1000 inhabitants is 3.[17] EPP has been reported worldwide, with prevalence between 1:75,000 and 200,000. Although the incidences of porphyrias are somewhat biased, depending on the type, all eight types are distributed worldwide. In Japan, by 2008 a total of 898 cases had been reported since the first case report in 1920.[18]

2.2.6 Gene Mutation and Diversity

ALA dehydratase (ALAD) deficiency porphyria (ADP), congenital erythropoietic porphyria (CEP), and hepatoerythopoietic porphyria (HEP) are autosomal recessive disorders. Patients with these porphyrias are clinically and biochemically homozygous, whereas their parents are clinically asymptomatic heterozygotes. In porphyrias, not only the autosomal recessive forms but also the autosomal dominant forms (acute intermittent porphyria (AIP), erythropoietic protoporphyria (EPP), hereditary coproporphyria (HCP), and variegate porphyria (VP)) do not result from a single mutation; in many cases they result from different mutations, depending on family lines. Such multiple mutations are as diverse as point mutations, additions, and deletions, with large numbers of mutation sites in each. Only rarely have homozygous cases been reported in heterozygous forms of autosomal dominant porphyria.

2.3 Acute Porphyrias

The acute porphyrias are AIP, VP, HCP, and ADP. When exposed to some environmental factor in addition to drugs or stresses, genetically predisposed people acutely or subacutely manifest multifarious symptoms of the gastrointestinal, neurologic, circulatory, endocrine, and metabolic systems (gene–environment interaction) (Table 2). For acute porphyrias, administration of large amounts of glucose is a common effective treatment. This is presumably because high doses of glucose suppress the activity of ALAS, the first enzyme in the heme biosynthetic

Table 2 Classifications of the acute porphyrias highlighting important clinical and epidemiological aspects at a glance[2)]

Acute porphyrias	incidence	Age of onset	Inportant aspects
Acute intermittent porphyria	0.5–1 per 100,000	second to fourth decade of life; very rarely before puberty	most common acute porphyria in the world; acute neuro-logical attacks but no photo-sensitivity/cutaneous symptons
Variegate Porphyria	approx. 1 per 300 in South Africa; relatively rare elsewhere	second to third decade of life; usually not before puberty	skin symptoms similar to PCT and acute attacks similar to AIP can occur (neuro-cutaneous porphyria); founder mutations identified in South Africa and Chile
Hereditary coproporphyria	very rare (<50 cases reported)	usually not before puberty	acute attacks similar to AIP and cutaneous symptoms including erythema and blistering can occur (neurocutaneous porphyria)
ALAD deficiency porphyria	extremely rare (<10 cases reported)	early and late onset have been described	neurological symptoms similar to AIP can occur; no photosensitivity/cutaneous symptoms

pathway, thereby reducing the production of porphyrin metabolites (the glucose effect).[19,20)] In these acute hepatic porphyrias have increased risks of hepatocellular carcinoma[21,22)] and chronic renal failure.[23)]

2.3.1 Acute Intermittent Porphyria (AIP)

1) Etiology and Symptoms

AIP is the most prevalent form of acute porphyria. In AIP, decreased porphobilinogen deaminase (PBGD) (hydroxymethylbilane synthase, uroporphyrinogen I synthase) activity and heme levels trigger the de-repression mechanism, leading to excretion of ALA and porphobilinogen (PBG) from the liver in large amounts. Extensive accumulation of ALA and PBG, in the acute phase of AIP, provokes gastrointestinal symptoms such as abdominal pain and vomiting, often accompanied by peripheral neuropathy manifested as numbness and adynamia of the extremities. Although abdominal pain is almost inevitable and severe, objective findings such as tenderness and muscular guarding are seldom observed, so that AIP often mimics ileus or even hysteria. Peripheral neuropathy is almost inevitable, causing such symptoms as adynamia and numbness of the extremities. In addition, central nervous system symptoms such as disturbance of consciousness and convulsion, as well as psychiatric symptoms such as anxiety, depression, delirium, and hallucination, may occur, sometimes leading to misdiagnosis as schizophrenia. In extremely serious cases symptoms of bulbar paralysis may occur; this can be fatal. Circulatory symptoms such as hypertension and tachycardia are also often noted early and clearly reflect the clinical course. In addition, abnormal lipid metabolism, disturbance of carbohydrate metabolism, thyroid dysfunction, ectopic and inappropriate secretion of antidiuretic hormone, and growth hormone abnormalities commonly occur. Most of these symptoms are based on abnormalities of the nervous system, including the autonomic nervous system. No cutaneous symptoms are noted.

2) Diagnosis and differentiation

When a female patient between puberty and middle age acutely or subacutely develops abdominal pain or peripheral neuropathy of unknown cause, an acute porphyria should be suspected and urinary ALA and PBG should be measured. The urinary PBG level remains elevated in remission. Healthcare providers should be aware early that AIP mimics acute abdomen and the like (Table 3), causing patients to be subjected to polysurgery. Being a very rare disorder with vague presentation, the diagnosis is often missed by clinicians.[8)]

Table 3 Initial diagnosis of acute porphyrias[8)]

Accute abdomen	Liver dysfunction
Ileus	Neuropathy
Appendicitis	Guillain-Barre syndrome
Psychogenetic disorders (hysteria)	Ovarian volvulus
Pancreatitis	Ectopic pregnancy
Epilepsy	Gallstone
Hyperemesis gravidarum	Others
Acute peptic ulcer	

3) Treatment and prognosis

AIP is treated by administering fluids and glucose in large amounts. Concurrently, individual symptoms are treated by symptomatic therapy. Extreme caution should be taken to ensure proper administration of medications. The prognosis of AIP is excellent as long as early diagnosis is performed and use of contraindicated medications is avoided.

2.3.2 Variegate Porphyria (VP)

In VP, the levels of all the porphyrins ranging from ALA to protoporphyrin XI (PPXI) are elevated because of a deficiency in PPOX (protoporphyrinogen oxidase). VP presents with medical and neurologic symptoms similar to those of AIP, as well as cutaneous symptoms similar to those of porphyria cutanea tarda (PCT); all of these can develop to different degrees. Acute and cutaneous symptoms are treated in accordance with the treatments for AIP and cutaneous porphyrias, respectively.

2.3.3 Hereditary Coproporphyria (HCP)

HCP presents mainly with acute symptoms similar to those of AIP, but HCP symptoms are often milder. HCP symptoms include cutaneous symptoms, which must be differentiated from those of VP. In severe cases (in homozygotes, enzyme activity is only 2% to 10% of normal), harderoporphyrin levels are increased in the urine and feces. In the acute phases, urinary ALA and PBG levels are increased, returning to normal in remission. Fecal crude protein levels are continuously elevated.

2.3.4 ALAD Deficiency Porphyria (ADP)

ADP is an extremely rare disease: only 7 cases have been reported to date worldwide. ADP is an inherited ALAD deficiency in which mutations of both alleles result in a decrease (to less than a few percent of normal) in hepatic ALAD activity, triggering overproduction of ALA. ADP symptoms, including diverse acute symptoms, are difficult to distinguish from those of AIP.

2.4 Cutaneous Porphyrias

The cutaneous porphyrias are CEP, EPP, HEP, and PCT, all of which present with broad spectra of symptoms of photosensitive dermatosis, as well as liver damage (Table 4).

Table 4 Classification of the cutanea porphyrias highlighting important clinical and epidemiological aspects at a glance[2)]

Cutanea porphirias	incidence	Age of onset	Important aspects
Porphyria cutanea tarda	most common porphyria worldwide	third to fourth decade of life; usually not before puberty	most frequent type of porphyria worldwide; acquired and hereditary variants exist; moderate to severe photosensitivity; cutaneous symptoms include vesicles and bullae, erosion, crusts, milia, scarring, hyperpigmentation, and hypertrichosis; undistinguishable from VP
Erythropoietic protoporphyria	second-highest incidence of the cutaneous porphyrias	early childhood (1–4 years); late onset extremely rare	cutaneous symptoms include erythema, edema, purpura, skin thickening, waxy scars; usually no blistering; in approximately 5% of the cases severe liver disease can occur
Congenital erythropoietic porphyria	very rare (aprrox. 150 cases reported)	infancy/first decade of life	very severe clicnical course; vesicles and bullae, erosions, excoriation, exulceratation, crusts, milia, scarring, hyperpigmentation, and hypertrichosis; mutilation; hemolytic anemia; hepatosplenomegaly; porphyrin deposition in bones and teeth (erythrodontia)
Hepatoerythropoietic porphyria	extremely rare (approx. 25 cases reported)	early infancy	recessive variant of PCT; reported in the USA and Europe; markedly increased photosensitivity and severe clinical course possible; vesicles and bullae, erosions, excoriation, crusts, millia, scaring, and hypertrichosis; mutilation can occur

2.4.1 Congenital Erythropoietic Porphyria (CEP) (Gunther's disease[24)])

CEP, which presents as the most severe photosensitivity of all the porphyrias, is one of the rarest diseases and is caused by the overproduction of type 1 isomer due to deficiencies in uroporphyrinogen III synthase (UROS). Skin bullae, which develop soon after birth, are severe and are accompanied by ischemia and red urine. In addition to skin lesions, CEP symptoms include finger contracture; nail

deformation; defects in the nose, ears, and fingers; hypertrichosis; erythrodontia (exhibiting red fluorescence of the teeth under UV irradiation); splenomegaly; hemolytic anemia; and scleral involvement. Some cases of late-onset CEP have also been reported. No effective therapy for CEP has been established.[25)]

2.4.2 Erythropoietic Protoporphyria (EPP)

1) Concept

EPP manifests as skin photosensitivity in infancy, characterized by pain, redness, and swelling immediately after exposure to sunlight. Liver damage is also common in EPP.[26)]

2) Etiology and Symptoms

In EPP, decreased ferrochelatase (FECH) activity produces excessive PPXI in the erythroblasts. PPXI appears in the red blood cells and plasma and is excreted from the liver to the bile and feces, resulting in skin sensitivity, cholelithiasis, and liver damage. Autopsy examination almost always shows hepatic cirrhosis but seldom shows bullae or cicatrization. Symptoms similar to those of angioedema, including stinging (burning), itching, erythema, and swelling, occur at the site of light exposure. Moreover, during the chronic phase, symptoms of skin rash, such as pigmentation, hypertrichosis, and linear scarring due to skin fragility, are commonly noted.

3) Diagnosis and Differentiation

In EPP, only PPXI levels in the blood and feces are markedly increased.

Detection of fluorescent erythrocytes (even in carriers) and recognition of light hemolysis serve as useful adjuncts to diagnosis. A liver biopsy sample of an EPP patient with concurrent liver damage shows red fluorescence under UV irradiation.

4) Treatment and Prognosis

To treat EPP, protection from light is of primary importance. In addition, administration of substances such as β-carotene, cholestyramine resin, cimetidine, hematin, and cholic acid, as well as plasmapheresis, has been attempted, but none has proved to be reliable. EPP patients free of liver damage have a relatively good prognosis.

2.4.3 Hepatoerythropoietic Porphyria (HEP)

HEP is one of the rarest forms of porphyria in the world and is characterized by abnormal porphyrin metabolism in both the liver and the bone marrow. HEP is considered a homozygous form of familial PCT (fPCT) because of the very low uroporphyrinogen decarboxylase (UROD) activity (7% to 8% of normal). HEP presents with severe photosensitive dermatosis as the main symptom, immediately after birth.[27,28)]

2.4.4 Porphyria Cutanea Tarda (PCT)

1) Concept

PCT is the most prevalent form of cutaneous porphyria and is characterized by abnormal porphyrin metabolism caused by reduced hepatic UROD activity of the fourth enzyme involuved in hepatic heme synthesis, accompanied by photodermatosis and liver damage. Two types of PCT are known: familial PCT (fPCT) and sporadic PCT (sPCT).[29)]

2) Etiology

Whereas fPCT is associated with mutations in the UROD gene, such mutations are not present in sPCT. The mechanism of action underlying sPCT is still unclear. In fPCT, UROD activity is almost lost because of a deficiency on one allele; thus only the enzyme activity from the normal allele is detected, resulting in a UROD activity of 50% of normal. However, there are many carriers who do not develop fPCT despite having the gene associated with fPCT; this suggests that the development of fPCT involves factors such as excessive intake of alcohol, estrogen, and iron, as may be the case in sPCT.[30)] Virus infection, such as hepatitis C and HIV, are also suspected of being contributing factors.[31)]

3) Symptoms and Examination

PCT characteristically presents with cutaneous symptoms such as solar dermatitis and skin fragility, facilitating the formation of bullae and thereby resulting in erosion, cicatrization, and pigmentation. In rare cases, such PCT symptoms are complicated by sclerodermatous changes. Liver damage occurs, with symptoms such as iron deposition, fat changes, necrosis, chronic inflammatory change, deposition of porphyrin-like needle crystals, and fibrosis; these are likely to lead to liver cirrhosis and liver cell carcinoma.

4) Diagnosis and Differentiation

fPCT is common in adult females, and sPCT in middle-aged males. Histopathological examination by skin rash biopsy characteristically shows deposition of periodic acid-Schiff (PAS)-positive substances around the blood vessels in the superficial dermis and bulla formation at the dermoepidermal interface, together with deposition of immunoglobulin and complement at the interface. Urine and liver biopsy samples exhibit red fluorescence under UV irradiation. Urinary uroporphyrin (UP) and heptacarboxyl porphyrin (7P) levels are increased.[32)]

5) Treatment and Prevention

In mild cases of PCT, urinary porphyrin levels return to normal only when the causal factors are eliminated. Phlebotomy is performed in patients with markedly high urinary levels of porphyrin. In addition, administration of deferoxamine as an iron chelating agent and of interferon in hepatitis C virus-complicated PCT has been reported to be effective.[33,34)]

2.5 Other Aspects of Abnormal Porphyrin Metabolism

It is widely known that abnormal porphyrin metabolism is triggered by many factors, including hepatic disorders, blood disorders, hypermetabolism, and endocrine disorders; poisoning with heavy metals such as lead; halogenated aromatic hydrocarbons such as dioxin and hexachlorobenzene (HCB); and numerous pharmaceuticals, such as phenobarbital, cetrimide, griseofulvin, and carbamazepine (Table 5).[35]

Table 5 Causes of secondary porphyrinuria

· ***Anemias***
Dys erythropoietic, Aplastic, Hemolytic, Pernisious
· ***Leukemias/lymphomas***
AML, CML, ALL, CLL, Hodgkin's disease
· ***Chemicals and drugs***
Barbiturates, benzens, estrogen, ethanol, carbamazepine, carbon tetrachloride, halogenated aromatic hydrocarbons, heavy metal (As, Pb, Hg etc), phenytoin, prosgestaens
· ***Hereditary conjugated hyperbilirubinemias***
Dubun-Johnson and Rotor's syndromes
· ***Liver disease***
Alchoholic, cholestatic, chronic hepatitis, chirrhosis, viral hepatitis (especially hepatitis C)
· ***Miscellaneous causes***
Blonze baby syndrome, diabetes mellitus, infentious diseases, myocardial infarction, pregnancy, staravation, etc

Secondary porphyrinurias are the most common causes of increased porphyrins in the urine. These increases are mild-to-moderate in degree (less than threefold above upper limit of normal), usually mainly due to coproporphyrins. Stool porphyrins are generally normal.
Abbreviations used: ALL, acute lymphocytic leukemia; ALM, acute myelocytic leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelocytic leukemia; As, arsenic; Hg, mercury; Pb, lead

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