Ⅲ．研究成果の刊行物・別冊

しみ 誤診？ 本当は ポルフィリン症

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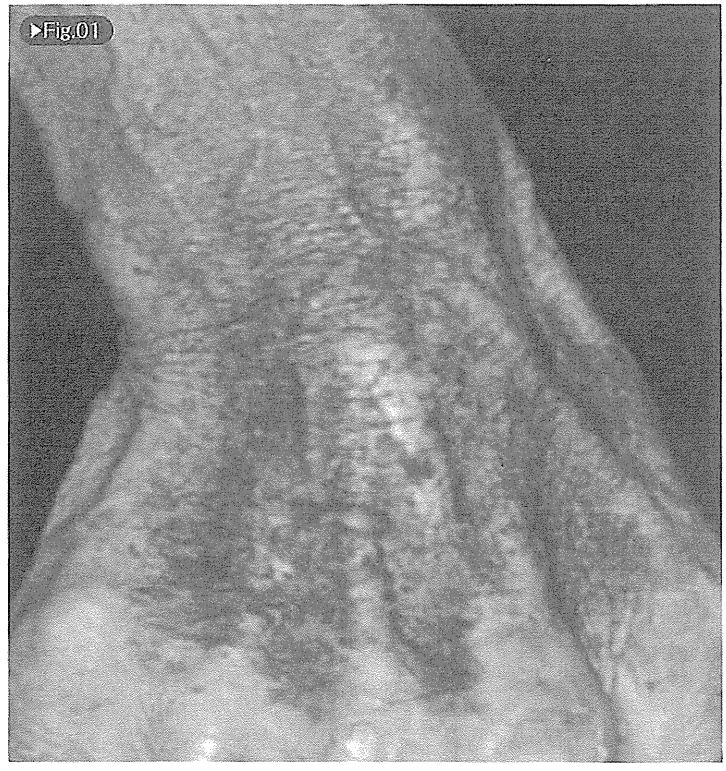
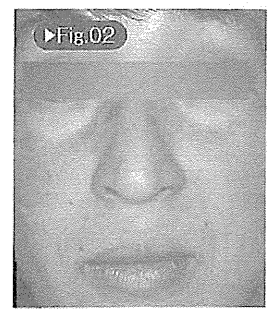


誤診されやすい背景

“しみ”という症候名は色素沈着をきたすさまざまな疾患に対して用いられる．したがって，背景となる病態も多岐にわたる．慢性に生じる非特異的な“しみ”をいかにして特異的診断に結びつけるかが重要であろう．

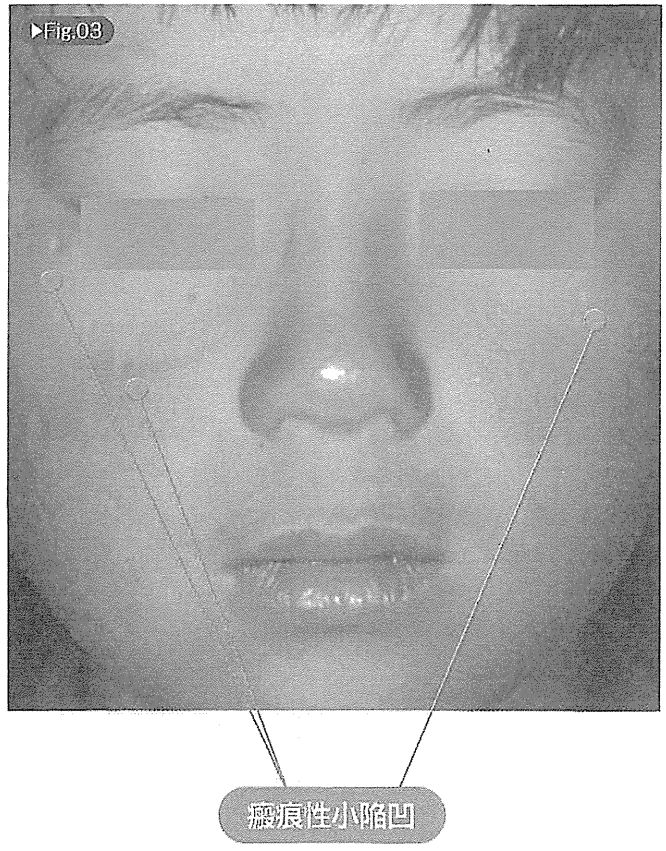
ポルフィリン症と誤診されやすいしみ（日光皮膚炎後色素沈着）とは

Fig.02 のようなびまん性の色素沈着を示す症例はポルフィリン症の除外が必要になる．光感作物質への曝露も考慮したほうがよい．



ポルフィリン症の臨床像

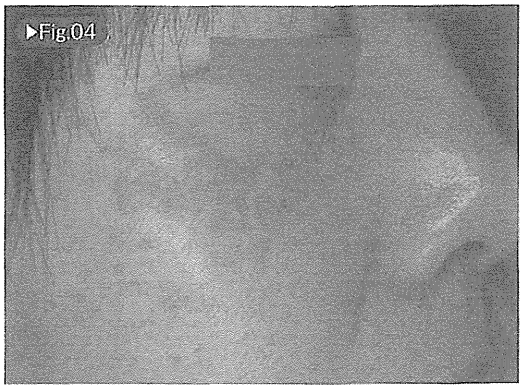
ポルフィリン症とはヘム合成系にかかわる複数の酵素のいずれかの活性低下によって，ポルフィリン体またはその前駆体が蓄積することによって光線過敏，神経症状，消化器症状などをきたす疾患群である．これらのうち骨髄性プロトポルフィリン症など多くは光線過敏が明らかな場合が多いが，異型ポルフィリン症は潜伏期にはほとんど症状がなく，ポルフィリン体も陰性か微増に留まることもあり注意を要する．ポルフィリン症でみられる色素沈着は通常びまん性であるが，組織障害がくり返されると Fig.01 のごとくしみ様所見を呈することがある．Fig.03 の症例は骨髄性プロトポルフィリン症．露光部に色素沈着がびまん性に生じている．陥凹性小瘢痕の存在が過去の水疱形成を示唆している．



鑑別疾患

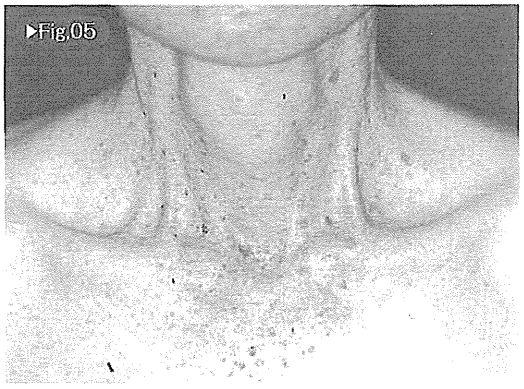
①しみ（肝斑）

中年女性の“しみ”としてありふれたものだが，色素斑と健常部の境界が明らかで，限局した色素沈着である．



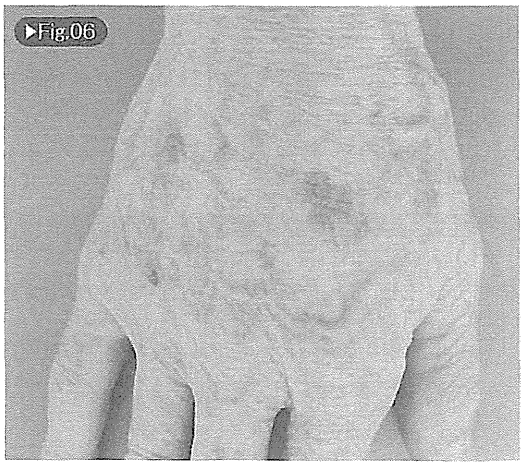
②しみ（色素性乾皮症）

顔面，頸部，および前胸部のいわゆるＶエリアに色素斑が散在しており，光線の影響であることが明らかであるが，皮疹の性状は点状，斑状の色素斑である．遺伝子診断によって色素性乾皮症と診断した．



③しみ（老人性色素斑）

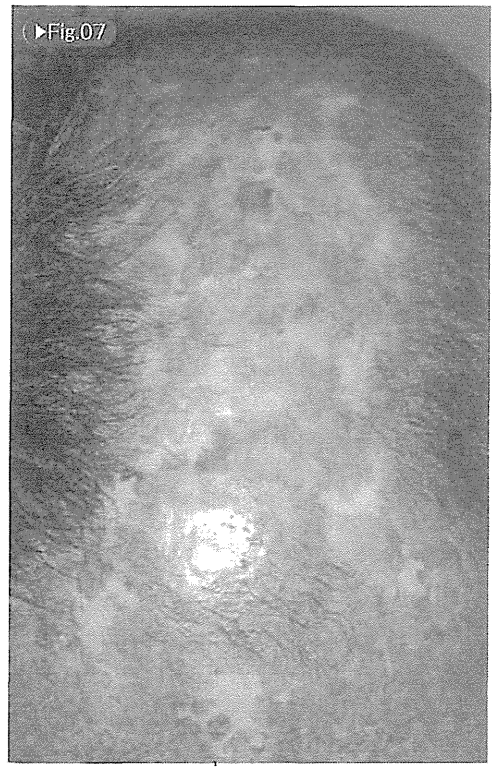
いわゆる“しみ”のひとつであり，過去の光線曝露が影響していることは間違いないが，これ自体でポルフィリン症が疑われることは通常ない．



ほかのポルフィリン症の皮膚症状を探す

Fig.01 の症例の頭部である．萎縮性の皮膚に点状の色素斑と脱色素斑が散在している．尿中ポルフィリン体が著明高値であり，晩発性皮膚ポルフィリン症と診断した．

（▶Fig.07



コアエッセンス

ポルフィリン症は急性の光線過敏ののちにびまん性色素沈着を生じるのが一般的であるが，慢性に経過して組織障害をくり返すと点状ないし斑状色素沈着を生じ，“しみ”のような所見を呈することがある．

Chapter 7

Eryhtropoietic Protoporphyria

Akira Kawada, Shigeru Kawara and Hajime Nakano

Additional information is available at the end of the chapter

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1. Introduction

The porphyrias are metabolism diseases caused by the deficiency of a specific enzyme in the heme biosynthetic pathway. Porphyrias have been classified into bone marrow and liver types on the basis of the predominant site of porphyrin production site. Recent classification of porphyrias shows acute porphyria and cutaneous porphyria according to the condition of signs (Table 1). Eryhtropoietic protoporphyria (EPP; OMIM 177000) is an autosomal dominant disease of porphyrin metabolism caused by decreased activity of the ferrochelatase (FECH; E.C. 4.99.1.1) that is the terminal enzyme in the heme biosynthetic pathway (Fig. 1). This type of porphyria was first described in 1953 by Kosenow and Treibs and this description was completed in 1961 by Magnus et al.[1] Decrease in FECH activity causes excess protoporphyrin induction, leading to photosensitivity of the skin and liver dysfunction. Photosensitivity starting from childhood makes quality of life low and liver dysfunction may lead to hepatic failure and death. In this session, we describe (1) clinical features of EPP, (2) genetic characteristics of EPP, and (3) mice models of EPP.

2. The clinical features of EPP

2.1. Skin

Suspicion of EPP should be raised by the history of screaming or skin pain in a child on going outdoors.[2] However, it is very difficult to suspect EPP if clinical manifestation are minimum. The characteristics of photosensitivity in EPP are first a burning, stinging sensation appearing immediately at sun exposure followed by erythema, edema and purpura.[1] We reported a 1-year-old male infant with EPP who showed only erythema after sun exposure (Fig. 2).[3] Infant patients are unable to complain the abnormal sensations and pain. Cutaneous signs are characterized with erythema, swelling, papules, vesicles, small blood blisters, crusts, and scars. Scar, the most distinct skin lesion, is small, polygonal or linear, depressed or slightly elevated (Figs. 3 and 4). With the progression of the disease and

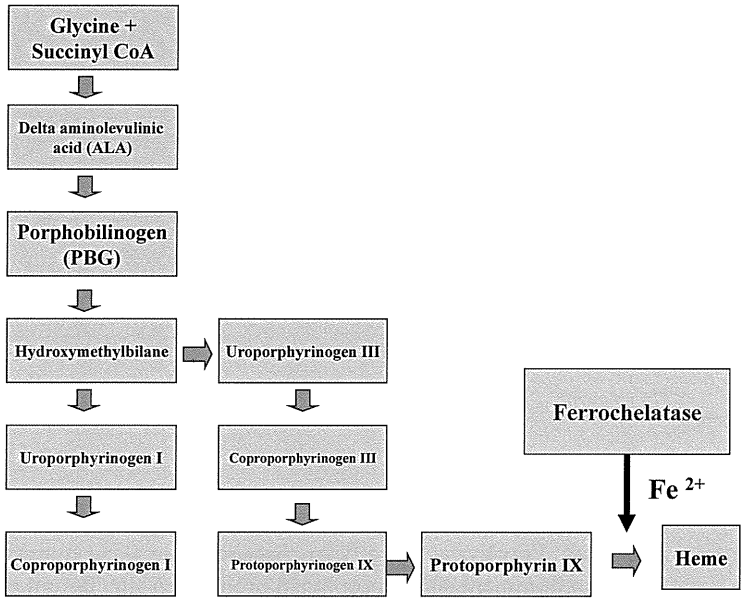

Figure 1. Heme biosynthetic pathway.

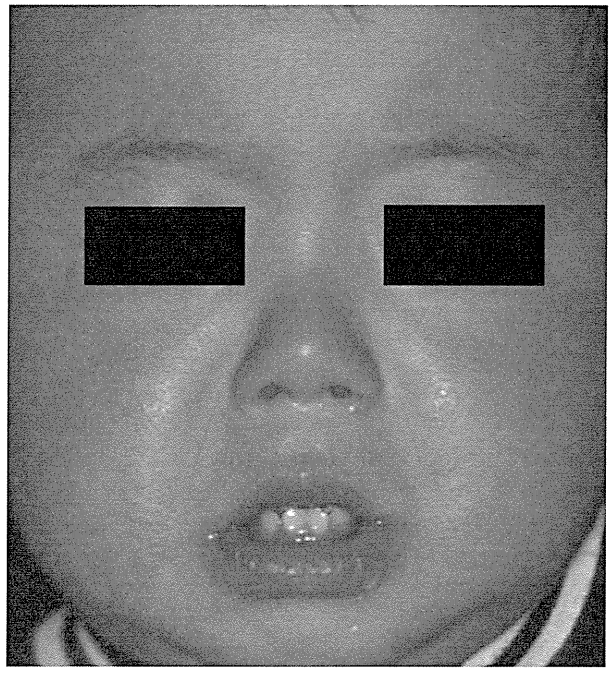

Figure 2. Clinical picture of a 1-year-old male baby with erythopoietic protoporphyria. Redness and swelling were seen on the face.

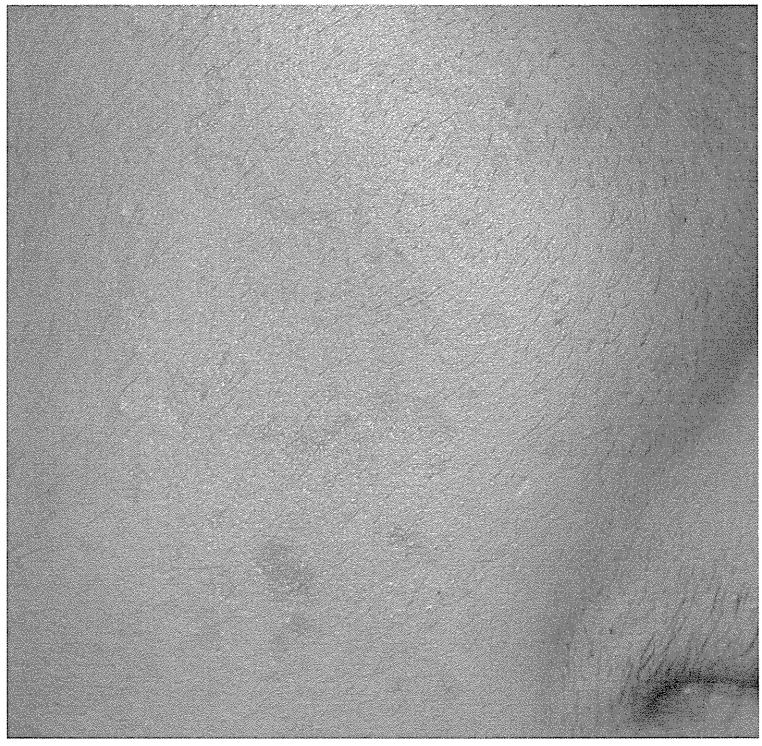

Figure 3. Clinical picture of a 14-year-old boy with erythopoietic protoporphyria. Depressed scars were seen on the face.

if sun exposure is not avoided, chronic lesions develop progressively with skin thickening (waxy lichenification on the dorsa of the hands) and scarring (pseudorhagades formation in the lips).[1]

Minder performed a systematic review of treatment options for dermal photosensitivity in EPP.[4] Sixteen of 25 relevant studies dealed with β-carotene. However, the results from β-carotene were strongly contradictory and efficacy was inversely correlated with study quality.[4] Afamelanotide, an a-melanocyte-stimulating hormone analogue, was reported to be effective for EPP.[5] Afamelanotide, making melanin density of the skin increase, was effective for photosensitivity from artificial light and sunlight in 5 EPP patients.[5] Moreover, Petersen reported that oral treatment with a high daily dosage of zinc sulphate during the spring and summer reduced light sensitivity and pain in 71% of 14 EPP patients.[6] They speculated that zinc treatment in EPP patients may have provided antioxidant protection of cellular membranes against the deleterious photodynamic effects of protoporphyrin IX (PPIX) accumulation.[6] Photoprotection against visible light that absorbs PPIX is still a mainstream in the care of EPP patients, although these novel approaches were reported. However, some reports raised awareness about vitamin D deficiency due to sun avoidance in EPP. Spelt reported that 46% of 48 Dutch EPP patients showed decreased level of serum

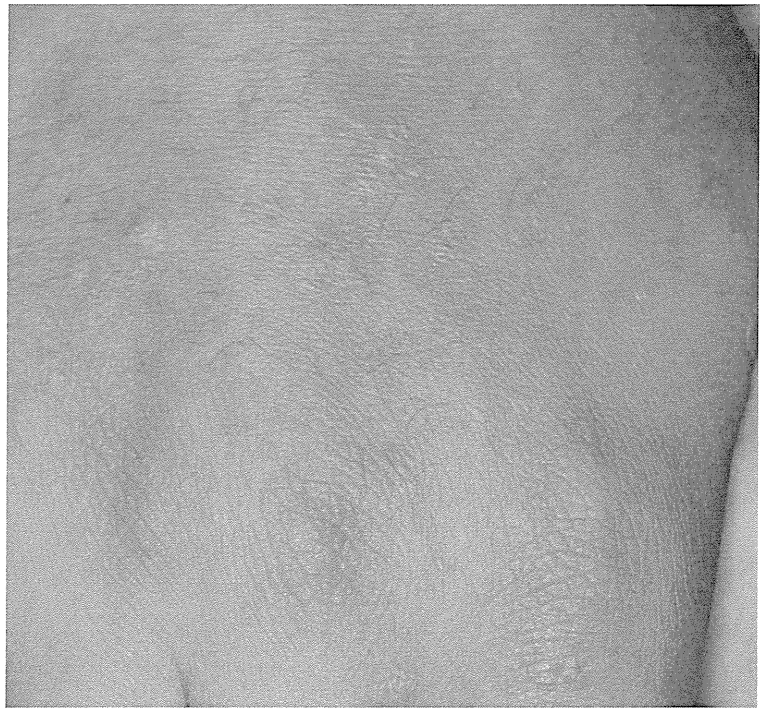

Figure 4. Clinical picture of a 14-year-old boy with erythopoietic protoporphyria. Whitish swelling scars were seen on the back of the hand.

25-hydroxyvitamin D.[7] Vitamin D deficiency was high in male patients and correlated with the severity of EPP.[7] Holme also reported that 17% was deficient and 63% was insufficient in serum 25-hydroxyvitamin D levels of 201 United Kingdom (UK) patients with EPP.[8] Then, we should care for vitamin D deficiency in EPP patients performing strict photoprotection.

2.2. Liver

Mild abnormalities of liver function may be detected in about 10% of patients of EPP and liver failure affects about 5-20%.[2, 9] Excess PP with any origin is excreted by the liver into bile and enters an enterohepatic circulation.[10] Excess PP becomes insoluble in bile and exerts cholestatic effects, structural changes from mild inflammation to fibrosis and cirrhosis.[10] Liver diseases include cholelithiasis, gallstones, biochemical abnormalities (aspartate amino transferase (AST), alanine amino transferase (ALT), gamma-glutamyl transpeptidase (gamma-GTP), alkaline phosphatase (ALP)), cirrhosis, and terminal liver failure. PP deposition in hepatocytes is invariable, whereas histological evidence of damage is less common; electron microscopy shows ultrastructural damage in most patients with EPP.[10]

Liver transplantation for liver failure in EPP patients started in 1980. Dowman investigated 5 UK cases receiving liver transplant for EPP-related liver diseases.[11] Two patients died at 44

and 95 months from causes unrelated to liver disease, while 3 patients were alive at 22.4 years, 61 months and 55 months after liver plant.[11] In spite of a good long-term survival, a high rate of postoperative biliary stricturing requiring multiple biliary interventions was seen.[11] Wahlin also investigated that 35 liver transplants for protoporphyric liver disease in 31 European patients between 1983 and 2008.[12] The overall rate of disease recurrence in the graft was high (69%), although they showed good survival rates, 77% at 1 year and 66% at 5 and 10 years.[12]

As liver transplant does not correct the constitutional deficiency of FECH, there is a risk of recurrence of liver disease even after liver transplant due to continuing overproduction of protoporphyrin.[9] Then, bone marrow transplantation may be considered in liver allograft recipients in the future.

2.3. Biochemistry and blood test

Increase of PP in the blood and stool is the most specific in EPP. However, urinary porphyris (uroporphyrin, coproporphyrin, porphobirinoge, δ-aminolevulic acid) remain as normal levels. Many patients with EPP have an apparent mild anemia with a microcytic hypochromic blood film.[2] However, administration of iron is not recommended since iron sometimes exacerbate the porphyria.

3. Genetic characteristics of EPP

EPP is a disease caused by decreased activity of the ferrochelatase (FECH; E.C. 4.99.1.1) that is the final enzyme in the heme biosynthetic pathway. The *FECH* gene contains 11 exons and spans about 45 kb of genomic DNA on chromosome 18q21.3, and its cDNA sequence encodes for 423 amino acids (GenBank no. D00726). The mode of inheritance is primarily autosomal dominant, and the clinical penetrance is low. In the dominant type of EPP, different degrees of enzyme deficiency are seen between patients and asymptomatic gene carriers, *i.e.*, symptomatic patients usually have less than 50% of the normal activity, whereas the asymptomatic ones show approximately 50% of the normal activity.[13]

Gouya reported that (1) coinheritance of a *FECH* gene defect and a wild-type low-expressed allele is generally involved in the clinical expression of EPP; (2) the low-expressed allelic variant was associated with a partial 5′ haplotype [-251G IVS1-23T IVS2μsatA9] that may be ancestral and was present in an estimated 10% of a control group of Caucasian origin; and (3) haplotyping allows the absolute risk of developing the disease to be predicted for those inheriting *FECH* EPP mutations.[13] Mutations of *FECH* gene in EPP are highly heterogenous and specific for each family members. Minder studied the association between "null allele" mutation and liver complication in 1112 EPP patients.[14] All 18 EPP patients who had severe liver complication showed a "null allele" mutation, whereas 20 patients with a missense mutation did not have liver complication till the time of study.[14] This study indicates that a significant genotype-phenotype correlation between "null allele" mutation and liver disorder in EPP.

Genetic variants in the *FECH* gene include more than 175 mutations and 538 single-nucleotide polymorphisms (SNPs).[15] The functionality of these SNPs may reduce the level of transcription of the *FECH* gene contributing to the triggering of EPP.[15] A common low expression allele, IVS3-48T>C, is seen in 10% of European Caucasians. Most EPP patients (~90%) have a *FECH* loss-of-function mutation *in cis* and the common low expression allele *in trans*, resulting in 15-25% of normal FECH activity.[16] As described above, mutations of *FECH* gene in EPP are highly family-specific. There have been many variations of *FECH* gene mutations reported in various countries.

Nakano firstly identified two novel mutations in two Japanese families using direct sequence analysis of the entire coding region of the FECH gene.[17] The proband in the first family was heterozygous for a 3-bp deletion from nucleotide positions 853 to 855 in exon 8, designated delCAA^{853}.[17] Pedigree analysis of the other family members showed that the mother and two sisters, all asymptomatic, were heterozygous for this mutation.[17] Restriction fragment polymorphism analysis indicated that the proband was homozygous for the IVS3-48C polymorphism, while other family members, asymptomatic carriers, had a wild-type T at position IVS3-48 in *trans* to the mutated allele.[17] They concluded that the IVS3-48C polymorphism in one allele and a deleterious mutation (delCAA^{853}) in the other allele caused a phenotype of EPP. In the second family, all three members having symptoms of EPP showed the C^{683}→T mutation in combination with the trans IVS3-48C polymorphism.[17] These results from the analysis of two Japanese families indicated that the intronic IVS3-48C polymorphism in the non-mutated allele is a distinct determinant of the EPP phenotype. Their further investigation of the frequency of IVS-48C polymorphism in 104 Japanese controls revealed that the genotypic frequency of IVS3-48C/C was 0.192, that was over 10 times those of European countries (0-0.017).[17] These differences may affect the prevalence and penetrance of EPP in Japan.

In UK, Whatley identified large deletions of the *FECH* gene in 19 (58%) of 33 unrelated UK patients with EPP using gene dosage analysis by quantitative PCR; (1) six deletions (c.1-7887-IVS1+ 2425insTTCA; c.1-9629-IVS1+ 2437; IVS2-1987-IVS4+352del; c.768-IVS7+ 244del; IVS7+2784-IVS9+108del; IVS6+2350-TGA+95del), (2) five breakpoints in intronic repeat sequences (AluSc, AluSq, AluSx, L1MC4), and (3) large insertion-deletion (Del Ex3-4).[18] Berroeta reported a UK case with late onset of EPP and identified a mutation (1001C→T; P334L).[19]

In Canada, Pierro identified a 10,376 bp deletion (c.1-7887_67+2422del) including a portion of the upstream intergenic region, the promoter, the exon 1 and a portion of intron 1 in a Canadian EPP patient of Italian origin.[20] Li also reported that a Canadian EPP patient had a novel large deletion [c.1-9628_67+2871del12566 bp] and three polymorphisms [c.1-251A>G, c.68-23C>T and c.315-48T>C] in trans to the deletion in *FECH* gene.[21]

In China, Zhou identified a novel IVS1+1G→C mutation of the FECH gene in a Chinese EPP family.[22] Fong identified a recurrent splice site mutation, c.67+1G>C, and a novel nonsense mutation, p.Y191X, in 2 unrelated Chinese families.[23] Their investigation revealed that the allele frequency of IVS3-48C in Hong Kong population (28%) was lower than that of

Japanese population but higher than that of European populations.[23] Ma identified a novel splicing *FECH* mutation, IVS3+1G→A, and IVS3-48C polymorphism in a Chinese EPP family.[24]

In Argentina, Parera detected three novel and two previously described mutations in five Argentinean EPP families; (1) a deletion (451delT) producing a stop codon located 18 codons downstream from the mutation, (2) IVS1-2A>G leading to exon 2 skipping, (3) IVS4-2A>G, which causes the loss of the first 48 bp of exon 5, (4) C343T, and (5) 400delA.[25] Colombo's study of 19 Argentina EPP patients identified three novel (p.S222N; p.R298X and p.R367X) and seven already known (g.12490_18067del; p.R115X; p.I186T; c.580_584delTACAG; c.598+1G>T; p.Y209X and p.W310X) and indicated the possibility of c.315-48C variant in *trans* to the mutated allele as a sufficient trigger of EPP.[15]

In Spain, Herrero reported that three novel mutations (IVS4+1delG, 347-351delC, and 130_147dupl 18) and IVS3-48C low-expression allele in ten of 11 EPP patients.[26] They also estimated the frequency of the IVS3-48C allele among 180 nonporphyric Spanish individuals as 5.2%.[26] In South Africa, Parker identified ten sequence variations; IVS3-48T / C polymorphism, five further polymorphisms, a 5-bp deletion in exon 7 (757_761delAGAAG), two previously described splice-site mutations (IVS3+2T>G and IVS7+1G>A), and a novel 7-bp deletion in exon 4 (356_362delTTCAAGA).[27] In Portugal, Morais identified heterozygosity for a novel mutation (c.1052delA) in *FECH* gene of two children, and heterozygosity for the hypomorphic allele IVS3-48T>C in two children and asymptomatic mother.[28]

Recently, an association of EPP and palmar keratoderma has been reported. Méndez detected a homozygous inheritance of a novel missense mutation Q285R, a homozygous A-to-G transition, c.854A>G, in the *FECH* gene in a Caucasian family of EPP associated with palmar keratoderma.[29] Minder also reported a case of an association of EPP and palmar keratoderma who had a novel homoallelic missense mutation (p.Ser318Tyr) in the *FECH* gene.[30] Their Palestinial (Jordanian) parents were heterozygous for the S318Y mutation.[30]

4. Mice models of EPP

Mice models of EPP are useful to investigate the effects of FECH on iron metabolism in EPP. Lyoumi investigated hematologic and iron status in FECH-deficient Fechm1Pas mutant mice.[31] Their mice had microcytic hypochromic anemia without ringed sideroblasts, little or no hemolysis, and no erythroid hyperplasia, whereas the mice showed no tissue iron deficiency but did a redistribution of iron stores from peripheral tissues to the spleen, with a 2- to 3-fold increase in transferrin expression of mRNA and protein levels.[31] Using Fechm1Pas mutant mice with the BALB/c and C57BL/6 backgrounds, Lyoumi demonstrated that BALB/c backgrounded Fechm1Pas mice had more severe cholestasis, fibrosis with portoportal bridging, bile acid regurgitation, sclerosing cholangitis, and hepatolithiasis as compared with the mice with C57BL/6 background.[32]

5. Conclusion

EPP is an autosomal dominant disease of porphyrin metabolism that is characterized with photosensitivity and liver disease. We have reviewed recent advances of clinical features of EPP, genetic characteristics of EPP, and mice models of EPP. Further studies of genetic analysis and FECH-deficient mice will provide us the new strategy for the treatment of EPP.

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先天性ポルフィリン症

SUMMARY

ポルフィリン症は，ヘム合成酵素活性の低下もしくは欠損による先天性または後天性の代謝異常と定義される．ヘム合成系の酵素は8種類存在し，最初の律速酵素であるδ-アミノレブリン酸合成酵素（ALAS）活性を除く，7種類の酵素に対応する病型が存在する．病態として肝性と骨髄性に分類される．全ポルフィリン症例の頻度からは，晩発性皮膚ポルフィリン症（PCT）に次いで赤芽球性プロトポルフィリン（EPP）が最も頻度が高い．第1番目の律速酵素であるALAS酵素の活性低下は鉄芽球性貧血と称して，ポルフィリン症例には含まれなかった．最近，ALAS活性は2種類が存在し，非赤芽球性の1型（ALAS1）と赤芽球性（ALAS2）の2型に分けられ，ALAS2（赤芽球性）活性と最後の8番目のフェロケラターゼ酵素（FeC）活性が同時に低下するX染色体プロトポルフィリン症（X-EPP）例が報告されていてトピックスになっている[1]．

代謝障害と病態

EPPは，ヘム合成酵素群の最後の8番目のフェロケラターゼ（FeC）の活性低下によって，不溶性で遊離性のプロトポルフィリン（PP）が赤血球，皮膚，肝臓，胆汁中に蓄積し，糞便中に排泄され症状を引き起こす病態である．FeC遺伝子（*FECH*）は18q21.3に局在し，11のエクソンから成る．EPPは10歳前後に発症し，小児科や皮膚科で診断され，肝障害のため内科や消化器科で治療される疾患である．

臨床病型と分類

ポルフィリン症は皮膚型ポルフィリン症として先天性赤芽球性ポルフィリン症（CEP），赤芽球性プロトポルフィリン症（EPP）に，肝性ポルフィリン症例としてALA脱水素酵素欠損症ポルフィリン症（ADP），急性間欠性ポルフィリン症（AIP），遺伝性コプロポルフィリン症（HCP），異型ポルフィリン症（VP），晩発性皮膚ポルフィリン症（PCT）に分けられる（表1）．

肝臓と骨髄の両方に異常のあるポルフィリン症として，肝赤芽球性ポルフィリン症（HEP）がある．EPPをはじめ，多くは常染色体優性遺伝形式をとるが，CEPとHEPとADPが常染色体劣性遺伝形式をとる．PCTは日本では散発性が多く，遺伝性PCTの報告はない．小児期発症はEPPが最も頻度が高い．

臨床症状と診断

EPPは，幼児期から小児期における光線過敏症状から発症する．日光曝露後，顔面や四肢などの露光部にかゆみやちくちくする痛みで発生する．褐色の日光曝露部に色素沈着，水疱，紅斑などがみられる．EPPの10～20%に肝障害がみられる．胆汁うっ滞では感染症にかかりやすく，不明熱があったら敗血症などを疑う．すべての日光過敏症と幼児期においては色素性乾皮症などとの鑑別が重要である．

①検査所見：一般検査では赤血球PPの測定が最も迅速で簡便である．PPは胆汁を経由して便中に排泄されるので，尿中ポルフィリン体を測定しても無意味である．EPPの鑑別診断として，皮膚症状を合併する肝性ポルフィリン症例において，VPでは便中PPとコプロポルフィリン（CP）が増加し，HCPではCPが増加するので，PPが増加するEPPと明確に鑑別できる．糞便中ポルフィリン体の測定は，日本では聖マリアンナ医科大学予防医学教室でのみ可能である．

②確定診断：EPPの確定診断には，欠損酵素であるFeCの遺伝子（*FECH*）解析が必要である．ヘテロの*FECH*遺伝子の変異でFeC活性は約50%低下するが，反対側アレルのイントロン3の遺伝子多型であるIVS3-48T>Cの存在があって初めて発症することが明らかにされた[2]．EPPの遺伝子診断は弘前大学皮膚科や鳥取大学で行っている．

表1　ポルフィリン-ヘムの生合成系

酵素	中間体	ポルフィリン症
ALA 合成酵素（ALAS）	グリシン+スクシニル CoA	X 染色体プロトポルフィリン症（X-EPP）
ALA 脱水素酵素（ALAD）	δ-アミノレブリン酸（ALA）	ALA 脱水素酵素欠損症ポルフィリン症（ADP）
ヒドロキシメチルビラン合成酵素（HMBS）	ポルホビリノーゲン（PBG）	急性間欠性ポルフィリン症（AIP）
ウロポルフィリノーゲンⅢ合成酵素（UROS）	[ヒドロキシメチルビラン]	先天性赤芽球性ポルフィリン症（CEP）*
ウロポルフィリノーゲン脱炭酸酵素（UROD）	ウロポルフィリノーゲンⅢ	肝赤芽球性ポルフィリン症（HEP）* 晩発性皮膚ポルフィリン症（PCT）*
コプロポルフィリノーゲン酸化酵素（CPO）	コプロポルフィリノーゲンⅢ	遺伝性コプロポルフィリン症（HCP）
プロトポルフィリノーゲン酸化酵素（PPO）	プロトポルフィリノーゲンⅨ	異型ポルフィリン症（VP）
フェロケラターゼ（FeC）	プロトポルフィリンⅨ（PP） +Fe ヘム	赤芽球性プロトポルフィリン症（EPP）*

*幼小児期発症ポルフィリン症.

治療

皮膚症状を繰り返し肝障害が進展すると致死的になるので，平素から徹底した遮光対策が最も重要である[3]．

EPP の作用波長は可視光線から長波長紫外線に存在するので，その対策が重要であり，紫外線カットの衣服や下着などが市販されている．紫外線吸収剤は 380 nm 以下の紫外線を主に遮断するため，微粒子酸化チタンなどの紫外線散乱剤を主成分とする日焼け止めが有効である．貧血に対しては，鉄剤は肝障害を悪化させることがあるので使用せず，輸血は安全とされる[3]．

内科領域では EPP の肝障害例を診る機会が多いが，決定的な治療法はなく，敗血症で細菌が同定されていれば，抗菌薬が著効する例がある[4]．細菌が同定されなくても抗菌薬が著効したという，ペニシリン G の大量投与例が報告されている[5]．肝移植の早期の対策も必要である．黄疸が進行してからでは難しい．

予後

日光遮断対策が必須であり，肝疾患の予防が生命予後の鍵を握っている．

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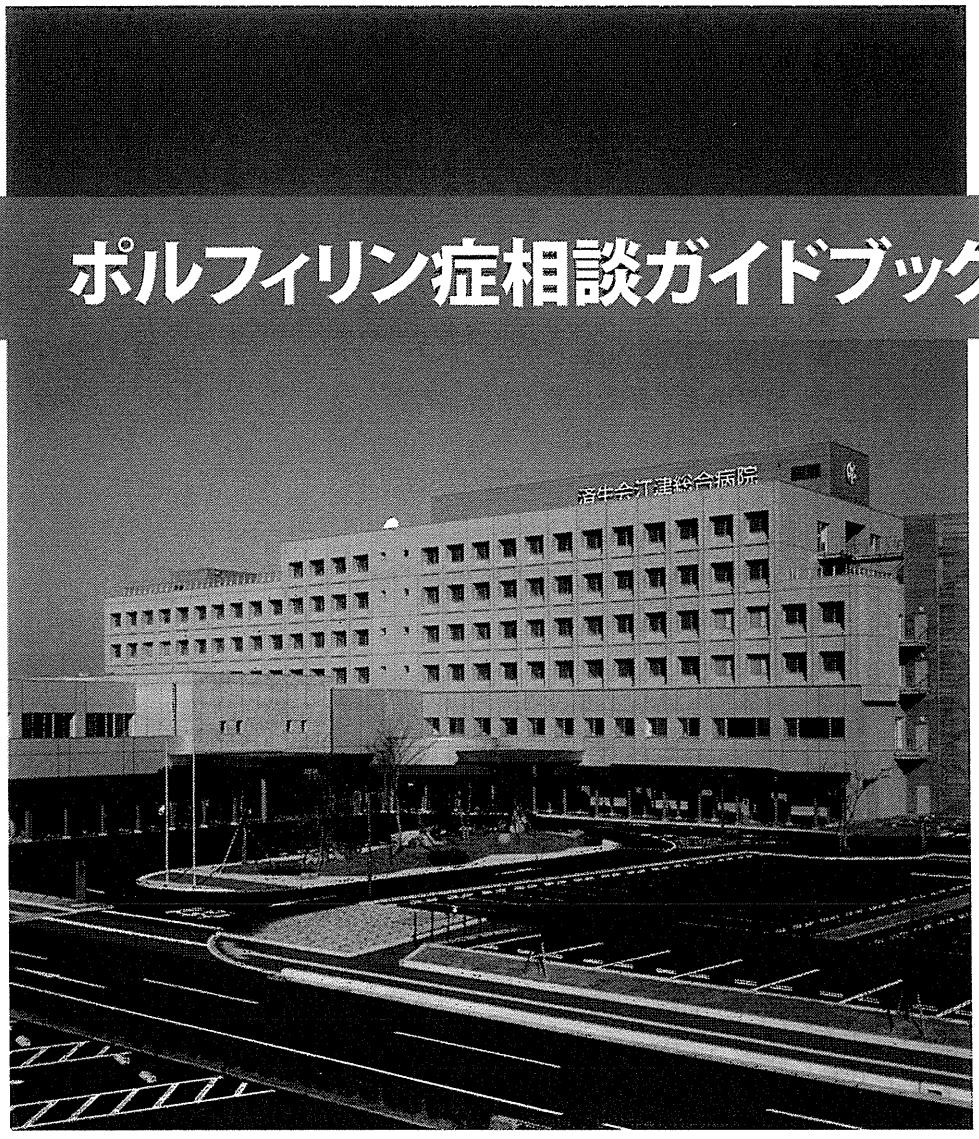
（堀江　裕）

難病疾患ポルフィリン症例の診断と治療に関する全国展開

ポルフィリン症相談ガイドブック



著者

平成24年度 社会福祉法人 恩賜財団済生会 医学・福祉共同研究

研究代表：堀江 裕（島根県済生会江津総合病院 院長）

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はじめに

ポルフィリン症患者さんを初めて診断したのは昭和５０年の１０月でした。２ヶ月を要して、「腹痛、高血圧、四肢麻痺」の４５歳の男性患者さんを、尿の色が濃いのに、肝機能検査が全く正常に近いのでなぜだろうかと疑ったのが最初です。

ポルフィリン症という病気があり、多彩な症状を呈することを知って、「検査法提要」という検査書をみながら、紫外線で照射して赤色に写しだされるポルフィリン尿を診た時の驚きは忘れられません。

平成１４年以来、ポルフィリン症例の相談窓口を開設して以来、全国から相談をうけ患者さんも江津まではるばる来院されるようになり、全国８０か所ある済生会のメリットを生かせないかと考えて、医学・福祉共同研究に応募して、若手の先生とのネットワーク造りをはじめました。

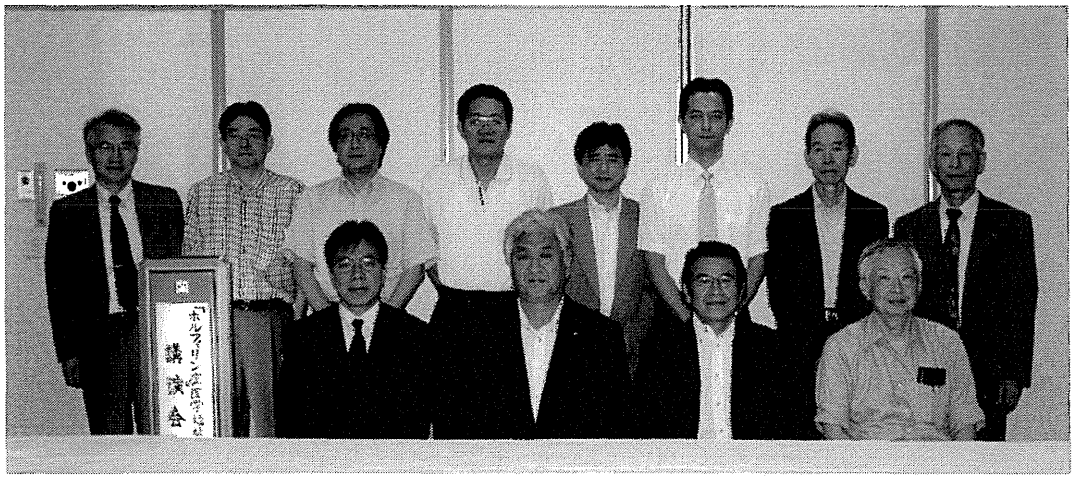
この冊子は相談を受けた内容を手直しして、わかりやすくまとめたものです。広く江湖に迎えられたら、うれしい限りです。

2013年3月

堀江　裕

済生会江津総合病院院長

今回の医学・福祉共同研究にご協力いただきました先生方



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