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A Girl with A Glowing Tooth : A Case of Congenital Erythropoietic Porphyria

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Abstract : **Congenital erythropoietic porphyria is a rare type of porphyria caused by inherited defects of uroporphyrinogen III synthase, an enzyme in the heme biosynthetic pathway. The resultant accumulation of porphyrins causes damage to the skin and erythrocytes, leading to cutaneous photosensitivity and hemolytic anemia. Furthermore, excess porphyrins are also deposited in tissues, bone, and teeth, resulting in a reddish-brown discoloration of the teeth (erythrodontia) which fluoresces under long-wavelength ultraviolet light. In this report, a case of a 9-month old infant girl with recurrent skin eruptions, anemia with hepatosplenomegaly, and erythrodontia is presented. The diagnosis of congenital erythropoietic porphyria was made based on the clinical manifestations and biochemical investigations. The patient was treated successfully with allogenic bone marrow transplantation and is still in remission after almost 3 years posttransplantation.**

เรื่องย่อ : ภาวะฟันเรืองแสงในผู้ป่วยเด็กหญิง: รายงานผู้ป่วย Congenital Erythropoietic Porphyria
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โรค congenital erythropoietic porphyria เป็นโรคพอร์ฟัยเรียชนิดหนึ่งที่พบได้น้อย เกิดจากการบกพร่องแต่กำเนิดของเอนไซม์ uroporphyrinogen III synthase ในกระบวนการสังเคราะห์ฮีม ส่งผลให้มีการสะสมของพอร์ฟัยรินในร่างกาย พอร์ฟัยรินที่คั่งจะทำให้เซลล์ของผิวหนังและเม็ดเลือดแดงมีการเสียหาย เป็นผลให้ผู้ป่วยมีอาการของผิวหนังแพ้แสงและภาวะซีดจากเม็ดเลือดแดงแตกง่าย นอกจากนี้พอร์ฟัยรินยังไปสะสมตามเนื้อเยื่อกระดูกและฟัน ซึ่งจะทำให้ฟันมีสีเปลี่ยนเป็นสีน้ำตาลแดง และเมื่อตรวจด้วยแสงเหนือม่วงจะพบว่าสามารถเรืองแสงได้ รายงานนี้ได้นำเสนอผู้ป่วยเด็กหญิงอายุ 9 เดือน ซึ่งมีประวัติและการตรวจพบที่สำคัญคือ มีผื่นตามผิวหนังเป็นๆ

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หายๆ ภาวะซีดร่วมกับมีตับและม้ามโต และมีฟันสีน้ำตาลแดง ผู้ป่วยได้รับการวินิจฉัยว่าเป็นโรค congenital erythropoietic porphyria โดยอาศัยอาการทางคลินิกและผลการตรวจทางชีวเคมี ผู้ป่วยรายนี้ได้รับการรักษาด้วยการปลูกถ่ายไขกระดูกเป็นผลสำเร็จ โดยอาการทางคลินิกของผู้ป่วยหายไปหลังได้รับการรักษาและยังไม่กลับเป็นใหม่หลังจากการปลูกถ่ายไขกระดูกแล้วเป็นเวลาเกือบ 3 ปี

INTRODUCTION

The porphyrias are a group of disorders resulting from deficiencies of the enzymes in the heme biosynthetic pathway. These lead to an accumulation of the toxic intermediates, i.e., porphyrin precursors and porphyrins, in the body. The clinical manifestations of porphyria are varied, ranging from dermatological (e.g. photosensitivity and skin fragility) to neurological involvements (e.g. abdominal pain, psychiatric symptom, and motor weakness). Because porphyria is relatively uncommon and may present with atypical medical or surgical history, the disease is often missed or wrongly diagnosed unless physicians are aware of the condition. Without proper diagnosis and treatment, the patients would suffer from morbidity and mortality associated with the disease. In this report, a case of female infant affected with a severe form of congenital erythropoietic porphyria (CEP) is presented. This type of porphyria is inherited as autosomal recessive and very rare; only one CEP case was previously reported in Thailand to date.[1] Nevertheless, the patient was promptly and correctly diagnosed as having CEP, and subsequently received bone marrow transplantation to treat the condition. This form of treatment has proved to be curative for CEP, but is not routinely considered for all CEP patients because of the high mortality risks associated with the procedure. However, in this patient, the treatment is considered successful so far because her clinical manifestations were completely resolved and she still remains in clinical remission after almost 3 years posttransplantation.

CASE REPORT

A 9-month old girl presented with a history of recurrent skin eruptions since she was 3 months old. Most of the skin lesions appeared on sun exposure areas. She was born at term and her birth weight was 2,500 g. She had normal developmental history. Her family had no consanguinity. Her mother noticed that she had erythrodontia and occasional reddish brown urine since birth. One month before coming to the hospital, she had anemia and abdominal distension. Physical examination showed body weight 6.9 kg (10^{th} - 25^{th} percentile), length 66.5 cm (10^{th} - 25^{th} percentile), head circumference 45 cm (90^{th} percentile), moderate pallor without jaundice, one dark brown lower incisor with coral red color under Wood's lamp (Figure 1B). Her abdomen was distended with hepatomegaly 1.5 cm and splenomegaly 10 cm. Multiple crusted lesions, 3 - 5 mm in diameter, with some areas of erythematous macules and hypopigmented atrophic scars 5 - 8 mm in diameter were present on her face, scalp, ears and forearms (Figure 1A). Other physical examinations were unremarkable. Complete blood count revealed hematocrit 25.6 %, mean corpuscular volume 71.1 fL, mean corpuscular hemoglobin 22.1 pg, reticulocyte 6.0 %. Some fragmented red blood cells, ovalocytosis, and polychromasia were seen. White blood cells and platelets were normal. Urine was reddish brown in color which turned to bright red color under Wood's lamp. Blood chemistry analysis revealed LDH 1,894 U/L, SGOT 221 U/L, and SGPT 131 U/L with normal ranges of other results. Bone marrow aspiration showed erythroid hyperplasia. Other investigations were unremarkable. Congenital erythropoietic porphyria was suspected and confirmed by the presence of a high level of uroporphyrinuria and coproporphyrinuria of 7,978 µg/L and 8,972 µg/L respectively (normal value 9.8 ± 9.6 and 78 ± 110 µg/L), and a high level of erythrocyte porphyrin of 787 µg/dL red blood cells (RBC) (normal value 50 ± 13.5 µg/dL RBC).

She was treated by supertransfusion to keep the average hematocrit of 40 % for a duration of 11 months. Her spleen and liver sizes were markedly reduced along with decreasing photosensitivity. At

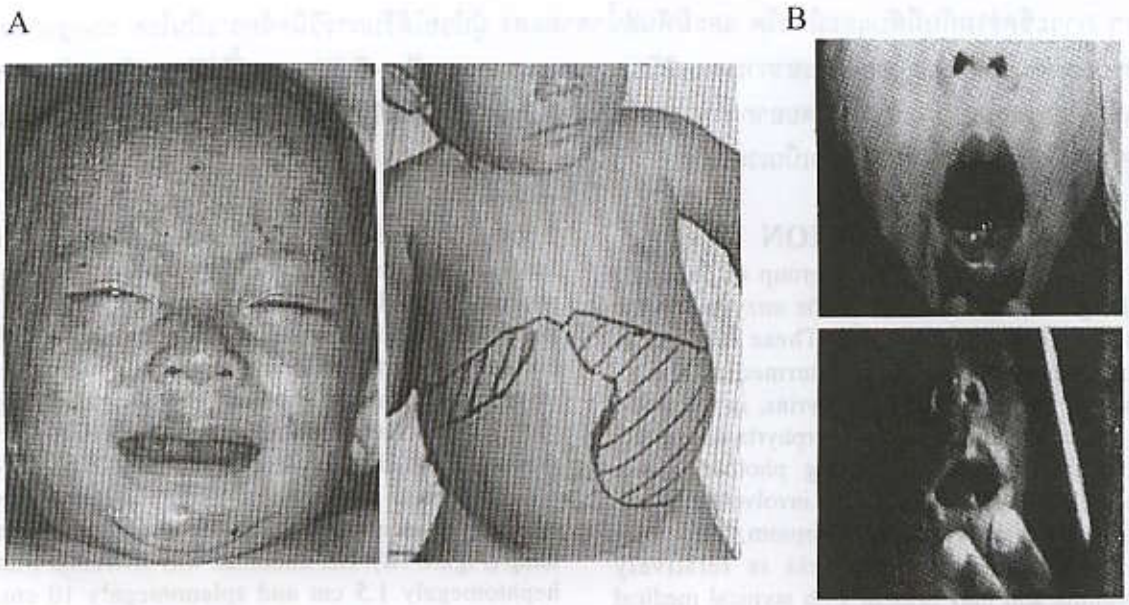

Figure 1. The clinical manifestations of the patient. A, cutaneous manifestation showing erythematous macules and hypotrophic scars on the face (left). The patient also had hepatosplenomegaly accompanying anemia (right). B, the lower incisor tooth showed a brown discoloration or erythrodontia (top), which fluoresced under a Wood's lamp (bottom).

the age of 1 year and 8 months, she underwent allogeneic bone marrow transplantation (BMT) from her 9-year old HLA-identical sister who was healthy. The preconditioning regimen consisted of busulfan and cyclophosphamide, followed by stem cell infusion of CD34+ 8.3 x 10^6 cells/ kg of the patient. Granulocyte colony stimulating factor was started on the following day. Graft versus host disease prophylaxis consisted of a short course methotrexate and 6 months of cyclosporin A. She had only mild complications during 1 month admission post BMT. One year post BMT, she developed purplish to gray macules with ill-defined borders at the face, shoulder, upper chest and abdomen. Skin biopsy was performed and a diagnosis of chronic graft versus host disease was made. She was treated with oral prednisolone for 8 months. Her erythrocyte porphyrin at that time was within the normal range of 50 µg/dL RBC.

Currently, 2 years and 10 months post BMT, she is healthy without anemia, hepatosplenomegaly or photosensitivity. Her urine is yellowish without changing in color postexposure to sunlight. Her urinary uroporphyrin and coproporphyrin are markedly reducing with time but still slightly high at 24 µg/L and 879 µg/L respectively. DNA analysis with short Tandem repeat markers of the patient were the same as those of the donor's.

DISCUSSION

The patient in this case had a history of recurrent cutaneous eruptions and anemia with hepatosplenomegaly. On physical examination, her tooth showed a dark brown discoloration (erythrodontia), which fluoresced under a Wood's lamp. In addition, her urine was dark brown and also gave bright red fluorescence under long-wavelength ultraviolet light. These findings indicated that there was an accumulation of excess porphyrins in the body, which were then deposited in the tooth and excreted into the urine. Thus, the patient was likely to be affected by a disease called porphyria. Porphyria

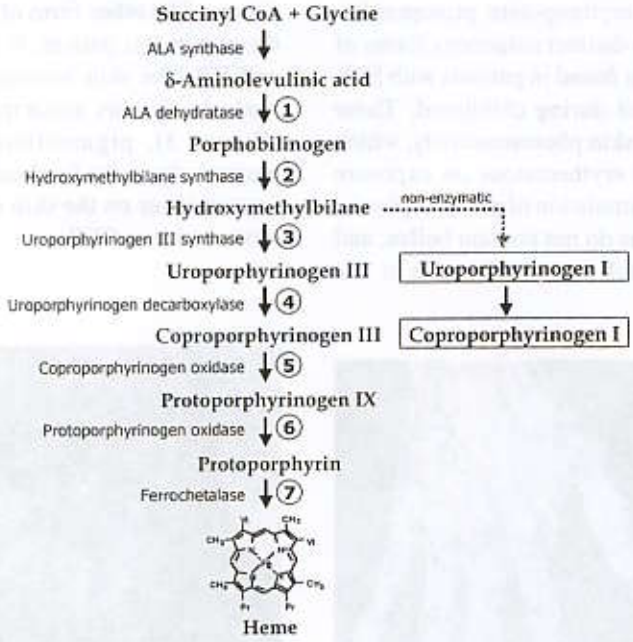

Figure 2. The heme biosynthetic pathway. Defects of the specific enzymes at various steps (shown in number) in the pathway result in different types of porphyria as follows; 1) ALA dehydratase deficient porphyria, 2) Acute intermittent porphyria, 3) Congenital erythropoietic porphyria, 4) Porphyria cutanea tarda, 5) Hereditary coproporphyria, 6) Variegate porphyria, and 7) Erythropoietic protoporphyria. Note that uroporphyrinogen I can be spontaneously generated from hydroxymethylbilane, and further processed into coproporphyrinogen I. These isomers I of porphyrins are elevated when there is a defect of uroporphyrinogen III synthase as found in congenital erythropoietic porphyria.

is a group of disorders in the heme biosynthetic pathway. There are seven main types of porphyrias arising from defects of the enzymes in the pathway as shown in Figure 2. The enzymatic deficiencies in the pathway result in an accumulation of porphyrins and porphyrin precursors, which are toxic and cause various clinical manifestations found in porphyria patients.

The clinical presentations in porphyria can be classified into acute (neuropsychiatric), cutaneous, and mixed forms. In the acute or neuropsychiatric form, the patients usually present with acute attacks after exposure to precipitating factors such as drugs, alcohol, or infection. The symptoms range from severe abdominal pain (most common), muscular weakness, mental changes, nausea, vomiting to convulsion and coma. This acute form is commonly found in acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), or variegate porphyria (VP), and it is usually associated with an increase of porphyrin precursors, i.e., porphobilinogen and/or δ-aminolevulinic acid. The pathogenesis of the clinical manifestations in the acute form is not clear, but possible mechanisms include damage by free radicals, direct neurotoxicity of aminolevulinic acid, and heme deficiency in nervous tissue.[2] However, the patient in this case was unlikely to suffer from AIP, HCP, or VP because her clinical features did not fit with those of the acute form and the symptoms of the above porphyrias rarely develop before puberty.

In this patient, one of the main presenting features was the cutaneous manifestation. The cutaneous form of porphyria is commonly found in congenital erythropoietic porphyria (CEP), porphyria

cutanea tarda (PCT) and erythropoietic protoporphyria (EPP). There are two distinct cutaneous forms of porphyria. The first one is found in patients with EPP, who are usually affected during childhood. These patients may have acute skin photosensitivity, which is burning, itching, and erythematous on exposure to sunlight due to an accumulation of protoporphyrin. However, the skin lesions do not contain bullae, and scarring is minimal, which was not the case in this patient. The other form of cutaneous porphyria, like the one in this patient, is found in CEP, PCT, HCP, and VP. The skin lesions include fragile skin that heals slowly after minor trauma, subepidermal bullae (Figure 3), pigmentation, and hypertrichosis, particularly on the forehead and upper cheeks. These lesions occur on the skin exposed to the sun and are most severe in CEP.

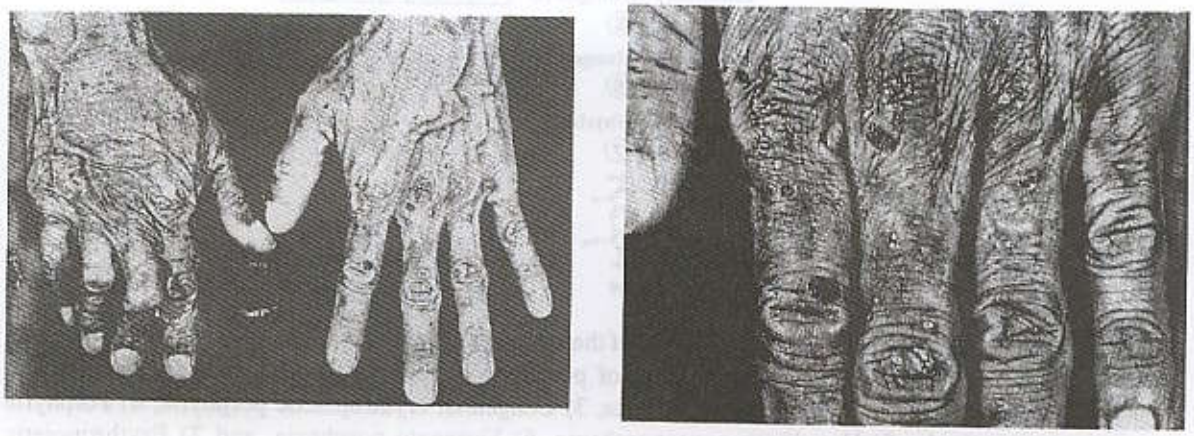

Figure 3. Typical cutaneous manifestations of CEP, PCT, HCP, and VP. The lesions usually occur on sun-exposed areas showing skin fragility, erosions, subepidermal bullae, and scars.

Of all cutaneous porphyrias, PCT is the most common (reviewed in[3,4]). It results from inherited or acquired defects of the enzyme uroporphyrinogen decarboxylase. PCT can be classified as either a sporadic or familial form. The majority of PCT is sporadic, accounting for 80-90% of cases. The decreased enzymatic activity is possibly due to the presence of inhibitors generated in liver cells.[3] Etiological factors include alcohol, oestrogens, iron, and chemicals (e.g. hexachlorobenzene). There is also an association with hepatitis C, HIV-infection. Mild iron overload is nearly always present. People with genetic hemochromatosis are four times more likely than otherwise normal subjects to have sporadic PCT, and these patients need to be investigated for iron overload, for example, ferritin and liver iron concentrations and DNA studies should be done for the coexistence of genetic hemochromatosis. Familial PCT is less common, accounting for approximately 10-20% of all PCT, and is inherited as an autosomal dominant trait. A rare and severe form of familial PCT called hepatoerythropoietic porphyria occurs in the patients harboring homozygous or compound heterozygous mutations of uroporphyrinogen decarboxylase enzyme, resulting in a marked reduction of the enzymatic activity (~5-10% of normal).

According to the clinical features of this patient, which included marked skin involvement and severe anemia at an early age, she could be affected with either hepatoerythropoietic porphyria or CEP (reviewed in[5]). Both types of porphyria have similar manifestations and are clinically indistinguishable.[6] Hepatoerythropoietic porphyria is a severe familial form of PCT as described above, whereas CEP is an autosomal recessive disorder resulting from a marked deficiency of uroporphyrinogen III synthase (Figure 2). The resulting accumulation of porphyrins in CEP causes damage to the skin and erythrocytes, leading to cutaneous photosensiti-

vity and hemolytic anemia, respectively. The severity and age at onset of CEP vary greatly, ranging from severe, infantile forms as seen in this patient to milder, later-onset forms, which have only cutaneous manifestations. Both CEP and hepatoerythropoietic porphyria are very rare disorders; only about 150 and 30 cases have been reported worldwide,[5,6] respectively.

To obtain an accurate diagnosis, appropriate biochemical investigations are very important because clinical features alone are not specific enough to be able to distinguish between the various types of porphyria. The aim of the biochemical tests is to analyze excess porphyrins or porphyrin precursors present in urine, feces, and plasma. However, in most laboratories, such analyses are not routinely performed or are impractical due to the lack of special instruments or experienced personnel. Therefore, simple screening tests such as examining the patient's urine under a Wood's lamp for coral-red fluorescence[7] or analyzing the spectrophotometric absorption at 400 nm[8,9] are useful in selecting the cases suspected of having porphyria for further investigations in the specialized laboratories.

The urine specimen from this patient was analyzed for δ-aminolevulinic acid, porphobilinogen, total uroporphyrin, and total coproporphyrin at the Department of Biochemistry, Faculty of Medicine Siriraj Hospital. The urinary levels of δ-aminolevulinic acid, and porphobilinogen were normal, whereas the total amount of uroporphyrin and coproporphyrin were highly elevated (~100- or 1,000-fold that of normal values). However, such spectrofluorometric analyses of total porphyrins,[10] which are routinely performed at the Department of Biochemistry laboratory, does not give any information about individual porphyrin intermediates, which accumulate differentially in various types of porphyria. For example, the urinary levels of both total uro- and coproporphyrin can be elevated either in CEP or PCT. However, a deficiency of uroporphyrinogen III synthase in CEP causes most hydroxymethylbilane to be non-enzymatically converted into uroporphyrinogen I instead of uroporphyrinogen III, resulting in an increase urinary excretion of the isomer I of uro- and copro-porphyrins respectively (Figure 2). In contrast, a deficiency of uroporphyrinogen decarboxylase in PCT interferes with the conversion of uroporphyrinogen III into coproporphyrinogen III, leading to an accumulation of the porphyrin intermediates such as hepta-, hexa-, and penta-carboxylic uroporphyrins. Therefore, several techniques, including high-performance liquid chromatography (HPLC)[11-13], have been developed to enable the separation and quantitation of porphyrins and their intermediates in order to help accurately differentiate various types of porphyria. During the past couple of years, the Department of Biochemistry laboratory has been setting up the HPLC method for quantitation of porphyrins[12,13] for clinical services, and it was used to reanalyze the urinary porphyrins from this patient. The results showed that the isomers I of uro- and copro-porphyrins were highly elevated, constituting > 95% of the total (both isomers I and III) of each porphyrin above (Figure 4), whereas in normal subjects, the isomer I of coproporphyrin is only ~20% of the total.[11] The urinary porphyrin profile was thus compatible with CEP, supporting the diagnosis in this patient.

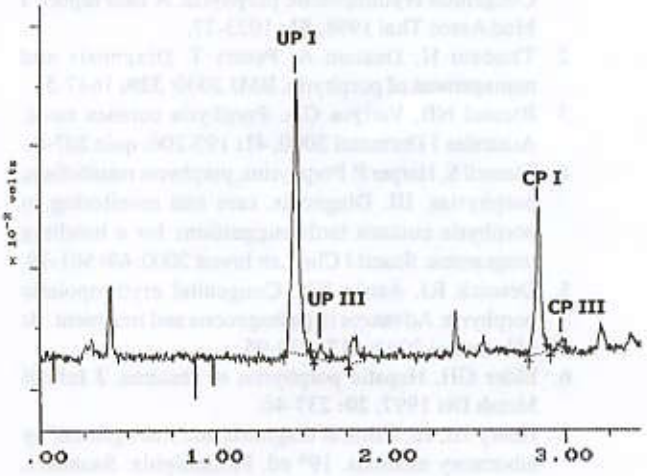

Figure 4. The HPLC analysis of urinary porphyrins. Various porphyrin isomers in the patient's urine are separated using HPLC techniques. In this patient, the isomer I of uro- and copro-porphyrins are highly elevated in disproportion to the isomer III porphyrins, compatible with the urinary porphyrin profile found in CEP. (UP and CP are uroporphyrin and coproporphyrin, respectively. The numeral I and III denote the isomers I and III of porphyrins).

Treatment for patients with CEP may be varied, depending on symptoms and disease severity. Skin lesions could be alleviated by skin protection with clothes and topical sunscreen to avoidance of sunlight. Prevention of infection and skin trauma is also important.[14] Large doses of beta-carotene was reported to make some improvement in tolerance to sunlight.[14,15] Erythrocyte transfusions transiently suppress erythropoiesis and decrease porphyrin excretion, which could decrease hemolysis.[14] Other methods of treatment have been used with varying short-term reductions in hemolysis, porphyrin excretion, and skin manifestations, such as hydroxyurea, splenectomy, intravenous infusion of hematin, plasmasorbent therapy with activated charcoal column and oral activated charcoal.[14-16] In severe cases, BMT has been proved to be the only treatment that can correct the enzymatic defect, resulting in a cure.[17] This patient received a successful BMT at the age of 1 year 8 months, which has completely corrected her cutaneous photosensitivity and hematologic manifestations for 2 years and 10 months. The levels of urinary uroporphyrin and coproporphyrin are markedly reduced post BMT but still slightly higher than normal ranges, presumably reflecting the abnormal porphyrin metabolism in extramedullary tissue such as the liver and kidneys.[18]

Although porphyria is relatively uncommon, particularly for CEP, awareness of the disease by physicians is vital for the patients to receive a prompt diagnosis and proper management, as was the case in this patient. With advances in biochemical investigations (e.g. enzymatic assays, genetic detection of the mutations) as well as in therapeutic managements for porphyria (e.g. BMT or even gene therapy), more porphyria patients can be saved from the morbidity or mortality associated with the disease.

REFERENCES

1. Chiewchanvit S, Mahanupab P, Vanittanakom P. Congenital erythropoietic porphyria: A case report. J Med Assoc Thai 1998; **81:** 1023-27.
2. Thadani H, Deacon A, Peters T. Diagnosis and management of porphyria. BMJ 2000; **320:** 1647-51.
3. Bleasel NR, Varigos GA. Porphyria cutanea tarda. Australas J Dermatol 2000; **41:** 197-206; quiz 207-8.
4. Thunell S, Harper P. Porphyrins, porphyrin metabolism, porphyrias. III. Diagnosis, care and monitoring in porphyria cutanea tarda-suggestions for a handling programme. Scand J Clin Lab Invest 2000; **60:** 561-79.
5. Desnick RJ, Astrin KH. Congenital erythropoietic porphyria: Advances in pathogenesis and treatment. Br J Haematol 2002; **117:** 779-95.
6. Elder GH. Hepatic porphyrias in children. J Inherit Metab Dis 1997; **20:** 237-46.
7. Henry JB, ed. Clinical diagnosis and management by laboratory methods. 19th ed. Philadelphia: Saunders, 1996.
8. Deacon AC. Performance of screening tests for porphyria. Ann Clin Biochem 1988; **25:** 392-97.
9. Deacon AC, Elder GH. ACP best practice No 165: Front line tests for the investigation of suspected porphyria. J Clin Pathol 2001; **54:** 500-7.
10. Schwartz S, Zieve L, Watson CJ. An improved method for the determination of urinary coproporphyrin and an evaluation of factors influencing the analysis. J Lab Clin Med 1951; **37:** 843-59.
11. Hindmarsh JT, Oliveras L, Greenway DC. Biochemical differentiation of the porphyrias. Clin Biochem 1999; **32:** 609-19.
12. Lim CK, Rideout JM, Wright DJ. High-performance liquid chromatography of naturally occurring 8-, 7-, 6, 5- and 4-carboxylic porphyrin isomers. J Chromatogr 1983; **282:** 629-41.
13. Lim CK, Rideout JM, Wright DJ. Separation of porphyrin isomers by high-performance liquid chromatography. Biochem J 1983; **211:** 435-38.
14. Sassa S, Kappas A. The porphyrias. In: Nathan DG, Orkin SH, eds. Nathan and Oski's Hematology of infancy and childhood. 5th ed. Philadelphia: W.B. Saunders Company, 1998: 463-79.
15. Badminton MN, Elder GH. Management of acute and cutaneous porphyrias. Int J Clin Pract 2002; **56:** 272-78.
16. Dawe SA, Peters TJ, Du Vivier A, Creamer JD. Congenital erythropoietic porphyria: Dilemmas in present day management. Clin Exp Dermatol 2002; **27:** 680-83.
17. Harada FA, Shwayder TA, Desnick RJ, Lim HW. Treatment of severe congenital erythropoietic porphyria by bone marrow transplantation. J Am Acad Dermatol 2001; **45:** 279-82.
18. Tezcan I, Xu W, Gurgey A, Tuncer M, Cetin M, Oner C, et al. Congenital erythropoietic porphyria successfully treated by allogeneic bone marrow transplantation. Blood 1998; **92:** 4053-58.