Congenital Erythropoietic Porphyria : A Case Report

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Abstract

Congenital erythropoietic porphyria is a rare autosomal recessive disorder of heme synthesis resulting from deficiency of uroporphyrinogen III synthase (UROIIIS). It is the most severe porphyria. The clinical manifestations are markedly variable due to the different mutation in the UROIIIS gene. We recently diagnosed a case of congenital erythropoietic porphyria.

A 9-year-old boy presented with recurrent ulcers on the skin especially dorsum of the hands and feet since aged 3. The physical examination revealed ulcers on the dorsum of the feet, mutilation of the fingers, fluorescent erythrodontia, and darkening and hypertrichosis of the sun exposed area. Laboratory findings showed mild hemolysis, red urine, increased serum alkaline phosphatase level, and fluorescence of the red blood cell and urine. The histopathology was consistent with porphyria. The urine and plasma porphyrin levels confirmed the diagnosis of congenital erythropoietic porphyria. The administration of oral ultracarbon and topical zinc oxide has been tried.

Porphyrias are the inherited metabolic disorders resulting from the accumulation of porphyrins. Congenital erythropoietic porphyria or Gunther's disease is inherited by autosomal recessive and characterized by severe photosensitivity, chronic hemolysis and massive porphyrinuria. It was demonstrated in the defect in the activity of uroporphyrinogen III synthase (UROIIIS, formerly termed uroporphyrinogen III cosynthase), the fourth enzyme of the heme biosynthesis pathway[1,2]. Uroporphyrin I is usually the predominant urinary and plasma metabolite[3]. It is the most severe porphyria. The clinical manifestations are markedly variable due to the different mutations in the UROIIIS gene[4]. Different mutations in the uropophyrinogen III synthase have been described since isolation of a full-length human cDNA encoding UROIIIS[5-11]. The severe patients are often trans-

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fusion dependent, while milder patients primarily have cutaneous involvement[7]. Although the onset usually occurs in infancy, the late onset of clinical features have occasionally been reported[12,13]. To the best of our knowledge, congenital erythropoietic porphyria has not been reported in Thailand. We recently diagnosed a case of congenital erythropoietic porphyria.

CASE REPORT

A 9-year-old Thai boy presented with recurrent skin ulcers especially on the dorsum of hands and feet since aged 3. He was the second child and delivered at term. His brother was 21 years old and healthy. There was no family history of photosensitivity or porphyria. His mother noticed that his urine had been red since birth. Physical examination revealed superficial ulcers with hemorrhagic crust on the dorsum of the feet (Fig. 1), mutilation of the fingers, mild splenomegaly, fluorescent erythrodontia, darkening and hypertrichosis of the sun exposed area. Laboratory findings showed hemoglobin 10.2 g/dl, hematocrit 33 per cent, WBC 3.7 x 10^9/L (polymorphonuclear cells 52%, lymphocytes 46%, and basophils 2%), and nucleated red blood cells 1/100 wbc. The urinalysis revealed wine-color urine, specific gravity 1.030, negative for protein and albumin, WBC 1-2/high power field, and RBC 1-2/high power field. The serum creatinine (1 mg/dl) was normal. The liver function test showed albumin 5.3 g/dl (3.5-5.0), globulin 4.2 g/dl (1.5-3.0), SGOT 39 U/L (5-40), SGPT 15 U/L (5-35) alkaline phosphatase 189 U/L (9-35), total bilirubin 0.8 mg/dl (0.5-1.5) and direct bilirubin 0.03 mg/dl (0.1-0.5). Peripheral erythrocytes were noted to have fluorescence with darkfield microscopy using blue-violet epilminescence. Urine-24 hour of volume 1150 ml was collected. Total plasma and urine porphyrin concentration were measured. The quantitative data are given in Table 1. The skin biopsy taken from a white papule on the dorsum of the right hand revealed PAS-positive homogeneous hyaline material around the blood vessels in the papillary and upper dermis and occasionally around eccrine ducts (Fig. 2). Electron microscopy showed multilayered basal lamina of dermal blood vessels (Fig. 3). These data confirmed the diagnosis of congenital erythropoietic porphyria. The administration of ultracarbon and topical zinc oxide have been tried.

Table 1. Total porphyrin values in urine and plasma of the patient.

Porphyrin levels	Urine (mcg/24 h)		Plasma (mcg/l)	
Uroporphyrin	1,530.65	(N < 40)	17,100	(N < 20)
Protoporphyrin	4,528.7	(N = 0)	706	(N < 20)
Coproporphyrin	848.7	(N < 280)	55.2	(N < 10)

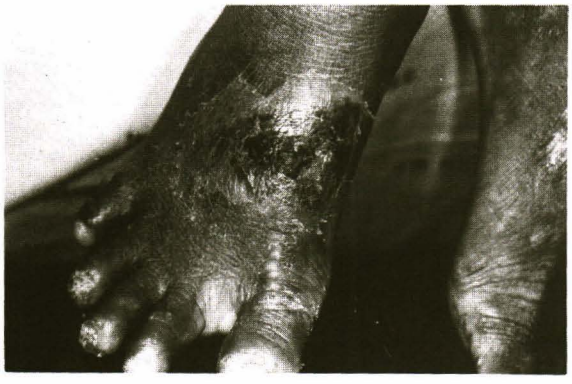

Fig. 1. Demonstrated ulcer with hemorrhagic crust on dorsum of right foot.

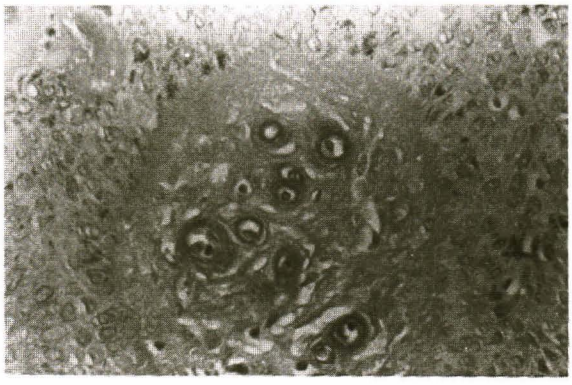

Fig. 2. The histopathology revealed PAS-positive material around the blood vessel walls in the papillary dermis (PAS with diastase, X400).

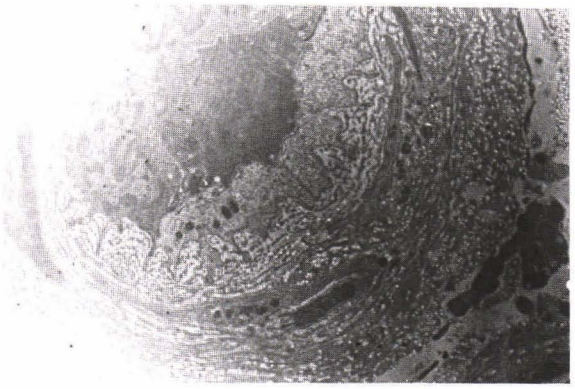

Fig. 3. The electron microscopy revealed multilayered basal lamina of a dermal vessel (X4000).

DISCUSSION

Congenital erythropoietic porphyria (CEP) is a rare autosomal recessive disease. Fewer than 200 cases had been reported until 1992[14]. It was classified into the cutaneous porphyria group. Typically the initial finding is a pink stain of diapers by urine and meconium[1]. Skin bullae, scarring on the face and hands, hirsutism, deposition of red-brown pigments in the bones and teeth, erythrodontia, red urine, massive excretion of porphyrin in the urine and hemolysis are typically found. Although erythropoietic protoporphyria (EPP) is the most common of the childhood porphyrias and presents with severe photosensitivity and fluorescent red blood cells. Hirsutism, hyperpigmentation and erythrodontia are unusual[1]. The biochemical data confirmed the diagnosis of erythropoietic porphyria in this patient. The other manifestations of congenital erythropoietic porphyria may include corneal and conjunctival changes, blepharitis,[15,16] osteodystrophy (characterized by sclerotic lesions and osteopenia with increased serum levels of alkaline phosphatase, fasting and total 24-hour urinary calcium excretion), soft tissue calcifications and widening of the diploic space, severe vertebral compression fracture, thoracic kyphosis and salt and pepper skull[17-20], hepatic failure, nephrotic syndrome and renal siderosis[21]. The prognosis is poor. Therapy is usually unstatisfactory and largely symptomatic. The treatments that have been described[22,23] include hypertransfusion, splenectomy, the administration of hematin[24], oral activated charcoal[25-28], hydroxyurea[29], low doses of chloroquine, bone marrow transplantation[30] and gene therapy[23,31,32]. Gene therapy would represent a great therapeutic improvement. Currently, it is not available in Thailand. Although, several reports of clinical remission with the treatment of activated charcoal have been shown. The result was not quite satisfactory in our patient.

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REFERENCES

1. Paslin DA. The porphyrias. Int J Dermatol 1992; 31:527-39.
2. Romeo G, Levin EY. Uroporphyrinogen III cosynthase in human congenital erythropoietic porphyria. Proc Natl Acad Sci U S A 1969;63:856-63.
3. Huang JL, Zaider E, Roth P, et al. Congenital erythropoietic porphyria: clinical, biochemical, and enzymatic profile of a severely affected infant. J Am Acad Dermatol 1996;34:924-7.
4. de Verneuil H, Moreau Gaudry F, Ged C, et al. Congenital erythropoietic porphyria. Apropos of a fatal case in the neonatal period due to acute hemolysis with hepatic failure. Arch Pediatr 1995;2:755-61.
5. Nordmann Y, Deybach JC, de Verneuil H, Boulechfar S, Grandchamp B. Point mutations in the uroporphyrinogen III synthase gene in congenital erythropoietic porphyria (Gunther's disease). Curr Probl Dermatol 1991;20:148-53.
6. Boulechfar S, Da Silva V, Deybach JC, et al. Heterogeneity of mutations in the uroporphyrinogen III synthase gene in congenital erythropoietic porphyria. Hum Genet 1992;88:320-4.
7. Warner CA, Yoo HW, Roberts AG, Desnick RJ.

Congenital erythropoietic porphyria: identification and expression of exonic mutations in the uroporphyrinogen III synthase gene. J Clin Invest 1992;89:693-700.
8. Warner CA, Poh Fitzpatrick MB, Zaider EF, Tsai SF, Desnick RJ. Congenital erythropoietic porphyria. A mild variant with low uroporphyrin I levels due to a missense mutation (A66V) encoding residual uroporphyrinogen III synthase activity. Arch Dermatol 1992;128:1243-8.
9. Bensidhoum M, Ged C, Hombrados I, et al. Identification of two new mutations in congenital erythropoietic porphyria. Eur J Hum Genet 1995; 3:102-7.
10. Xu W, Warner CA, Desnick RJ. Congenital erythropoietic porphyria: identification and expression of 10 mutations in the uroporphyrinogen III synthase gene. J Clin Invest 1995;95:905-12.
11. Tanigawa K, Bensidhoum M, Takamura N, et al. A novel point mutation in congenital erythropoietic porphyria in two members of Japanese family. Hum Genet 1996;97:557-60.
12. Murphy A, Gibson G, Elder GH, Otridge BA, Murphy GM. Adult-onset congenital erythropoietic porphyria (Gunther's disease) presenting with thrombocytopenia. J R Soc Med 1995;88:357P-8P
13. Horiguchi Y, Horio T, Yamamoto M, Tanaka T, Seki Y, Imamura S. Late onset erythropoietic porphyria. Br J Dermatol 1989;121:255-62.
14. Bickers DR, Pathak MA, Lim HW. The Porphyrias. In : Dermatology in general medicine, Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KF, eds, McGraw-Hill, New York, 1993: 1854-93.
15. Ueda S, Rao GN, LoCascio JA, del Cerro M, Aquavella JV. Corneal and conjunctival changes in congenital erythropoietic porphyria. Cornea 1989; 8:286-94.
16. Oguz F, Sidal M, Bayram C, Sansoy N, Hekim N. Ocular involvement in two symptomatic congenital erythropoietic porphyria. Eur J Pediatr 1993;152:671-3.
17. Ito M, Mayashi K, Uetani M, Isomoto I, Irifune H. Skeletal abnormalities in a case of congenital erythropoietic porphyria. Br J Radiol 1990;63: 891-3.
18. Pullon HW, Bellingham AJ, Humphreys S, Cundy TF. The osteodystrophy of congenital erythropoietic porphyria. Bone 1991;12:89-92.
19. Oliveri MB, Mautalen C, Mega M, Rossi E. Congenital erythropoietic porphyria: skeletal manifestations and effect of pamidronate treatment. Bone 1994;15:101-4.
20. Laorr A, Greenspan A. Severe osteopenia in congenital erythropoietic porphyria. Can Assoc Radiol J 1994;45:307-9.
21. Lange B, Hofweber K, Waldherr R, Scharer K. Congenital erythropoietic porphyria associated with nephrotic syndrome and renal siderosis. Acta Paediatr 1995;84:1325-8.
22. Kauppinen R, Timonen K, Mustajoki P. Treatment of the porphyrias. Ann Med 1994;26:31-8.
23. Moreau Gaudry F, Mazurier F, Bensidhoum M, Ged C, de Verneuil H. Metabolic correction of congenital erythropoietic porphyria by retrovirus-mediated gene transfer into Epstein-Barr virus-transformed B-cell lines. Blood 1995;85:1449-53.
24. Rank JM, Straka JG, Weimer MK, et al. Hematin therapy in late onset congenital erythropoietic porphyria. Br J Haematol 1990;75:617-8.
25. Tishler PV, Winston SH. Rapid improvement in the chemical pathology of congenital erythropoietic porphyria with treatment with superactivated charcoal. Methods Find Exp Clin Pharmacol 1990;12:645-8.
26. Hift RJ, Meissner PN, Kirsch RE. The effect of oral charcoal on the course of congenital erythropoietic porphyria. Br J Dermatol 1993;129:14-7.
27. Minder EI, Schneider Yin X, Moll F. Lack of effect of oral charcoal in congenital erythropoietic porphyria (letter). N Engl J Med 1994;330:1092-4.
28. Tanigawa K, Namba H, Ohtsuru A, et al. Plasmasorbent therapy with activated charcoal column for congenital erythropoietic porphyria (letter). Dermatology 1994;188:329-30.
29. Guarini L, Piomelli S, Poh Fitzpatrick MB. Hydroxyurea in congenital erythropoietic porphyria (letter). N Engl J Med 1994;330:1091-2.
30. Kauffman L, Evans DI, Stevens RF, Weinkove C. Bone marrow transplantation for congenital erythropoietic porphyria. Lancet 1991;337:1510-1.
31. de Verneuil H, Ged C, Boulechfar S, Moreau Gaudry F. Porphyria: animal models and prospects for cellular and gene therapy. J Bioenerg Biomembr 1995;27:239-48.
32. Moreau Gaudry F, Ged C, Barbot C, et al. Correction of the enzyme defect in cultured congenital erythropoietic porphyria disease cells by retrovirus-mediated gene transfer. Hum Gene Ther 1995;6:13-20.

รายงานผู้ป่วย 1 ราย ที่ป่วยเป็นโรคอีรีย์โธรปอยอีติค พอร์ฟัยเธียแต่กำเนิด

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โรค congenital erythropoietic porphyria เป็นโรคถ่ายทอดทางพันธุกรรมแบบ autosomal recessive ซึ่งพบได้น้อยมาก โรคนี้เกี่ยวข้องกับความผิดปกติในการสร้างฮีมเนื่องจากขาดเอ็นซัยม์ Uroporphyrinogen III synthase (UROIIIS) และจัดเป็นโรค porphyria ที่มีอาการรุนแรงที่สุด อย่างไรก็ตามโรคนี้ก็มีลักษณะอาการรุนแรงแตกต่างกัน เนื่องจากความผิดปกติของยีนที่ควบคุมการสังเคราะห์เอ็นซัยม์นี้เกิดที่ตำแหน่งต่างกัน รายงานนี้เป็นรายงานผู้ป่วย congenital erythropoietic porphyria 1 ราย

ผู้ป่วยเด็กชายไทยอายุ 9 ปี มารับการรักษาเนื่องจากมีแผลเป็นหายๆที่ผิวหนังโดยเฉพาะบริเวณหลังมือและหลังเท้ามาตั้งแต่อายุ 3 ปี ตรวจร่างกายพบมีแผลที่บริเวณหลังเท้า, นิ้วมือถูกทำลายจนเสียรูป, ฟันแดงซึ่งเรืองแสงเมื่อฉายด้วยแสงอุลตราไวโอเลต และผิวหนังบริเวณนอกร่มผ้ามีสีคล้ำและขนดก การตรวจทางห้องปฏิบัติการพบมีเม็ดเลือดแดงแตกเล็กน้อย ปัสสาวะสีแดง ระดับซีรั่ม alkaline phosphatase สูงกว่าปกติ และตรวจพบมีการเรืองแสงของเม็ดเลือดแดงและปัสสาวะเมื่อฉายด้วยแสงอุลตราไวโอเลต ผลการตรวจพยาธิสภาพที่ผิวหนังเข้าได้กับโรค porphyria ผลการตรวจระดับ porphyrin ในพลาสมาและปัสสาวะเข้าได้กับโรค congenital erythropoietic porphyria ได้ให้การรักษาผู้ป่วยด้วยยา ultracarbon ชนิดรับประทานและยาทาซิงค์ออกไซด์

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