□ Case Report □

A case of alkaptonuria : the first case in Korea

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Alkaptonuria is a rare metabolic disease in which homogentisic acid cannot be metabolized due to a lack of the enzyme homogentisic acid oxidase. The disease often manifests itself in childhood by darkening of the urine upon standing. The disease leads to such serious consequences as ochronosis of cartilage and connective tissues with arthritis. It is expected that treatment with ascorbic acid and a dietary restriction of protein may decrease the late and serious consequences by diminishing the serum concentration of the metabolite benzoquinone acetic acid. A thirteen month-old girl was recently diagnosed with alkaptonuria by urine organic acid analysis. She excreted pinkish urine on a diaper and as time went by the urine color changed to a light brown. In laboratory findings, urine examination and culture results were normal. But urine organic acid analysis detected abnormal findings a prominent and massive elevation of homogentisic acid. The other physical findings were normal. This is the first case diagnosed in Korea. **(Korean J Pediatr 2006;49:329-331)**

Key Words : Dark urine, Alkaptonuria, Ochronosis

Introduction

Alkaptonuria is a rare metabolic disease caused by deficiency of the enzyme homogentisic acid oxidase[1-3]. It is characterized by dark discoloration of the urine, ochronosis, and the brownish black pigmentation of eyes, skin, joints and some vital organs like heart and kidneys[3]. The condition commonly presents itself in adulthood. There have been no reported cases in Korea. However, we recently came upon thirteen month-old girl whose dark discoloration of urine led to diagnosis of the disease.

Case Report

This thirteen month-old female baby was doing well without any problems. She was born with a gestational age of 39 weeks, via normal vaginal delivery in birth weight 3.26 kg, at Soonchunhyang University Chunan Hospital. She was bottle fed formula milk. She was the only baby of healthy parents of a non-consanguineous marriage. There was recorded no family history of metabolic disease. At nine months, she first excreted pinkish urine on a diaper, and her urine was examined for urinary tract infection at a local clinic. Urine examination detected nothing, and culture results were normal. She was fed large amounts of water, and her urine color became normal gradually. One week later, she again excreted pinkish urine on a diaper, and as time went by the urine color changed to a light brown (Fig. 1).

On physical examination, her vital signs were stable (blood pressure 100/60 mmHg, pulse rate 124/min, respiratory rate 34/min, body temperature 36.9℃). Her height, weight, and head circumference were within normal ranges. She had no abnormalites or pathologic findings in skin,

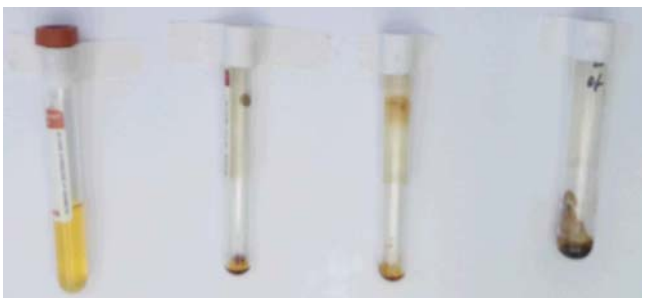

Fig. 1. Urine samples of normal person, parents and patient.

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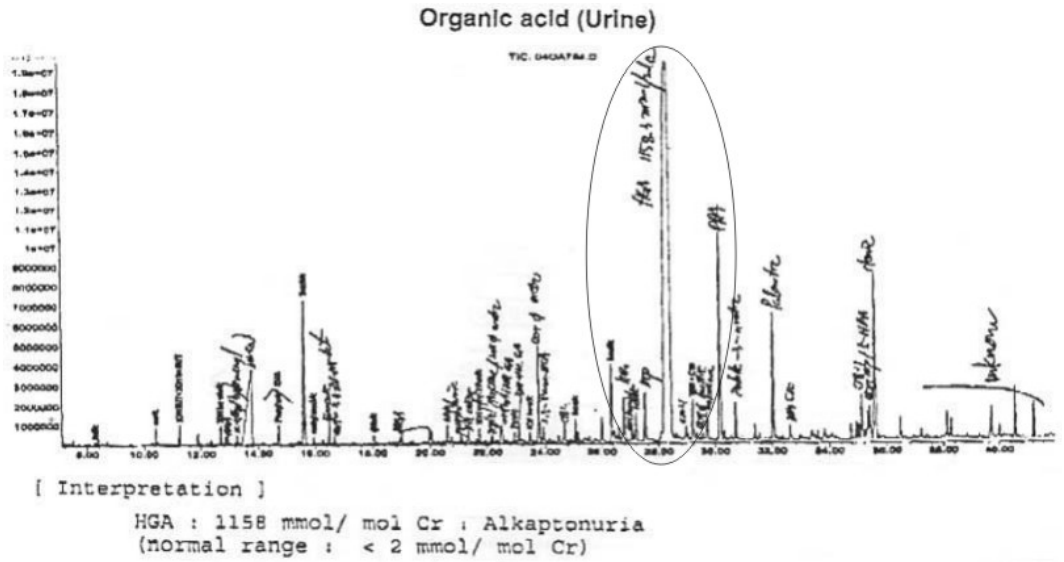

Fig. 2. Urine organic acid analysis for our patient. A large amount of homogentisic acid measured in the urine.

head and neck, eyes, chest, abdomen, back and extremities. She was normal, too, per neurologic examination.

Laboratory examination showed a white blood cell count of 13,600/mm^3 with platelets 236,000/mm^3, a hemoglobin level of 10.5 g/dL, hematocrit 30%. The results of the blood chemistry were AST 47 IU/L, ALT 23 IU/L, BUN 14.6 mg/dL, creatinine 0.4 mg/dL, PT 11.5 sec (INR : 0.95), aPTT 29 sec, and CRP 3.1 mg/L (normal range : <5.0 mg/L). Urine analysis showed nothing unusual and urine culture was normal. Amino acid analysis showed normal results. Detected abnormal finding was a prominent and massive elevation of homogentisic acid 1,158.3 mmol/molCr (normal range <2 mmol/molCr) (Fig. 2). Urine organic acid analysis was rechecked, but yield the same result (910.7 mmol/molCr).

Her case was followed up at Soonchunhyang University Hospital's outpatient department. She exhibited no abnormal findings now, except the light brown urine.

Discussion

Alkaptonuria is a very rare disease. It is the result of a deficiency of homogentisic acid oxidase, an important enzyme in the catabolism of aromatic amino acids. This deficiency prevents the breakdown of homogentisic acid finally to fumaric and acetoacetic acids. There is a buildup of oxidized and polymerized homogentisic acid throughout the body[1-3], more so in fibrous and cartilaginous tissue. This in turn leads to a brownish black melanin-like pigmentation, a phenomenon known as ochronosis[2, 3].

One of the first symptoms of alkaptonuria is the darkening of the urine upon standing[4]. However, the urine is of normal color when fresh. This phenomenon is due to the oxidation and polymerization of homogentisic acid. It is also pH-dependent and hence in some patients with alkaptonuria it is never seen if their urine has an acidic pH[5]. Dark urine stains on the diaper are sometimes the first telltale sign of the disease in infants[4]. Darkening of the urine is the only feature suggestive of alkaptonuria in the pediatric age group in most patients[2, 3]. In our case it started at the age of nine months and that was the presenting feature of the disease. Apart from the above phenomenon, the patient is usually asymptomatic until the third or fourth decade. Other main features of the disease include ochronosis and arthropathy. There appears bluish black or grayish blue pigmentation of the outer ocular tissues like the sclera and cornea and conjunctiva. Scleral pigmentation(Osler's sign) starts around the third decade[3-6].

Skin pigmentation usually appears around the fourth decade of life. One of the first sites to be involved is the ear cartilage, which becomes thickened with bluish black pigmentation[7]. Tendons show similar discoloration and this is demonstrated by telling the patient to make a fist upon which there is discoloration of the extensor tendons over the knuckles[4, 5]. There may be widespread dusky discoloration of the skin of the cheeks, forehead, axillae, and gen-

italia[7]. The buccal mucosa and larynx can be discolored, too[5]. Nails can be stained brown.

Other system can also be involved. There may be signs of aortic or mitral valvulitis. There may be prostatic or kidney stones.

Ochronotic arthropathy is a particularly troublesome feature and appears insidiously around the fourth decade resembling osteoarthritis[5, 6]. There is involvement of weight-bearing joints like the spine and knees as well as the shoulders. Detecting and measuring the amount of homogentisic acid in the urine confirms diagnosis of this disease. This is done by enzymatic spectrophotometry or gas liquid chromatography[8].

Treatment of alkaptonuria is frustrating. It involves giving a low-protein diet with restriction of phenylalanine and tyrosine[3]. However, this is not a very practical measure. Ascorbic acid is given in doses of 1 g/day[7-9] to reduced connective tissue damage. Presumably, the ascorbic acid with its antioxidant properties helps to retard the process of conversion of homogentisate to polymeric material then deposited in cartilaginous tissues[3, 4]. The course of the disease remains the same. The average lifespan of the patient is unchanged and he (she) dies of causes comparable with the general population[3-5].

This case of alkaptonuria is unique for its appearance at such a young age. The patient's mother noticed the darkening of the urine. Urine organic acid analysis confirmed the diagnosis.

한 글 요 약

한국에서 최초로 발견된 알캅톤뇨증 1례

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알캅톤뇨증은 상염색체 열성으로 유전하는 드문 질환으로 homogentisic acid oxidase 결핍에 의해 homogentisic acid가 체내 축적되고 소변으로 다량 배설되는 대사 이상 질환이다. 주로 도미니카 공화국과 슬로바키아에서 보고되고 있으나 한국에는 아직 보고된 바 없다. 증상으로는 소아 때에는 주로 배뇨 후 시간이 지나면 소변 색이 검어지는 특징이 보이고, 나이가 들면서 연골과 결체 조직의 착색, 관절염, 갈색증, 심장 질환, 신장 질환 등이 발생할 수 있다. 특별히 효과가 입증된 치료제는 없는 것으로 보고되고 있고, 진단은 뇨유기산분석을 통해 할 수 있다. 저자들은 내원 당시 13개월이었던 여자 환아에서 기저귀에 묻은 소변이 시간이 지나면서 연분홍 갈색빛을 보여 시행한 뇨유기산분석에서 homogentisic acid (normal range <2 mmol/molCr)가 1,158.3 mmol/molCr로 현저한 증가 소견을 보여 보고하는 바이다. 재검사에서도 역시 910.7 mmol/molCr 로 증가된 소견을 보였으며 환아 신체 어디에서도 연갈색이나 검은색의 착색된 부위를 찾을 수 없었다. 환아는 현재 ascorbic acid 투여하며 추적관찰 중이다.

References

1) Richard EB, Robert MK, Hal BJ. Nelson textbook of pediatrics. 17th ed. : Saunders 2004:403-4.
2) Archibald EG. The incidence of alkaptonuria : A study in chemical individuality. Lancet 1902;13:1616-20.
3) Karl SR. Alkaptonuria. Emedicine.com Available from : http://www.emedicine.com/ped/topic64.htm : July 2, 2005.
4) Sarkany RP, Breathnach SM, Seymour CA, Weismann K, Burns DA. Metabolic and nutritional disorders. Textbook of Dermatology. 7th ed. Oxford : Blackwell Science 2004;3:81-3.
5) Goldsmith L. Disorders of metabolism. Dermatology in General Medicine. 3rd ed. New York : McGraw-Hill Book Co, 1987;1642-6.
6) Soker CS, Cevik R, Aksunger A, Unlu K, Ava S. Ocular ochronosis : A case report and clinical findings. Acta Ophthalmol Scand 2002;80:340-2.
7) Lubics A, Schneider I, Sebok B, Havass Z. Extensive bluish gray skin pigmentation and severe arthropathy. Endogenous ochronosis. Arch Derma 2000;33:239-48.
8) Seegmiller JE. An enzymatic spectrophotometric method for the determination of homogentisic acid in the plasma and urine. J Biol Chem 1961;236:774-7.
9) Haas V, Carbasius EC, Klerk JB, Bakker HD, Smit GP, Huijbers WA, et al. The success of dietary protein restriction in alkaptonuria patients is age-dependent. J Inherit Metab Dis 1998;21:791-8.