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Case report-Olgu sunumu

Three case reports of alkaptonuria, a rare metabolic disease, in two first-degree relatives and one patient

İki akraba ve bir hastada nadir bir metabolik hastalık olan alkaptonürili üç olgu sunumu

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Abstract

Alkaptonuria is a rare hereditary disease, characterized by an abnormal blackish coloration of the urine, dark pigmentation of the connective tissue which is due to a deficiency in homogentisate 1, 2-dioxygenase (HGO), a tyrosine catabolizing enzyme. In this study two-years-old girl, five-year-old boy siblings and 11-month-old boy with alkaptonuria were presented. The diagnosis was confirmed by urinary homogentisic acid (HGA) amount. Normal levels of HGA in urine are 2.4 – 12 ng/ml. In these three cases within urine samples, the level of HGA (2.5-dihydroxyphenylacetic acid) showed an increase of 14, 14, 24 fold, respectively. The treatment focuses upon these aspects: correction of the production of HGA and prevention of complications. For reduction of HGA excretion has been suggested treatment with vitamin C and protein restriction have been proposed. Our patients were showed normal growth and development and no major complications of the disease because of consuming a diet with low protein.

Key words: Alkaptonuria, homogentisic acid (HGA), ochronosis

Özet

Alkaptonuri, tirozini katalizleyen homogentisat 1, 2-dioxygenase (HGO) enziminin eksikliğine bağlı, bağ dokusunda koyu pigmentasyon artışı ve idrarın siyahımsı anormal renk değişimi ile karakterize kalıtımsal nadir bir hastalıktır. Bu çalışmada, tanıları idrar homogantisik asit miktarı ile doğrulanan, alkaptonurili beş yaşında bir erkek çocuk ve iki yaşındaki kız kardeşi ile akrabaları olmayan 11 aylık bir erkek çocuk hasta sunuldu. Bu üç olgunun idrar örneklerindeki homogentisik asit (HGA) seviyelerinde sırasıyla 14, 14 ve 24 kat artış gösterildi. Hastalığın tedavisi HGA üretiminin düzeltilmesi ve komplikasyonlarından korunma üzerine yoğunlaşmıştır. HGA atılımının azaltılması için C vitamini tedavisi ve diyette protein alımının kısıtlanması önerilmektedir. Hastalarımızın diyetlerindeki düşük protein tüketimi nedeniyle büyüme-gelişmeleri normaldi ve hastalığın ana komplikasyonları bulunmuyordu.

Anahtar sözcükler: Alkaptonuri, homogentisik asid, okronozis

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Introduction

Alkaptonuria is a rare hereditary disease, characterized by an abnormal blackish coloration of the urine, dark pigmentation of the connective tissue which is due to a deficiency in homogentisate 1, 2-dioxygenase (HGO), a tyrosine catabolizing enzyme [1-3].

The excretion of homogentisic acid has increased in the urine samples of these patients. The disease leads to serious consequence, such as ochronosis of cartilage and connective tissues with arthritis [1-4]. We present here three patients (two siblings and an another patient) with alkaptonuria.

Patients

In this study two years old girl, five-year-old boy siblings and 11-month-old boy with alkaptonuria were presented. Their past history revealed that from early age a gradual dark discoloration had been noticed in their diapers but routine urinalysis had not revealed abnormalities. Two siblings' parent was a first-degree cousin; the parents of other boy were a third degree cousin. There were no abnormal findings on physical examination. The anthropometric measurements were as follows: length 92 cm (90 %), 112 cm (75 %), 75 cm (50-75 %); weight 14.5 kg (90 %), 22.5 kg (90 %), 10.7 kg (75%) respectively.

Laboratory findings included white blood count, hemoglobin level, BUN, creatinine and x-ray examination of thorax were normal. Sodium hydroxide was added to freshly passed three patient's urine. The urine color turned dark within a few minutes. There were initially diagnosed as having alkaptonuria by the presence of positive for urinary sodium hydroxide test. The diagnosis was confirmed by urinary homogentisic acid (HGA) (2,5-dihydroxyphenylacetic acid) amount. Normal levels of HGA in urine are 2.4 – 12 ng/ml. In these three cases within urine samples, the level of HGA showed an increase of 14, 14, 24 fold respectively (Table 1).

Table 1. Urinary 2,5-dihydroxyphenylacetic acid (HGA) levels in three alcaptonuric patients (GS/MS).

Patients	Urinary HGA Internal Standard (130 mmol/mol cre)
I (two-year-old girl)	Increased 24 fold (2,5-dihydroxyphenylacetic acid)
II (five-year-old boy)	Increased 14 fold (2,5-dihydroxyphenylacetic acid)
III (eleven-month-old boy)	Increased 14 fold (2,5-dihydroxyphenylacetic acid)

Discussion

Alkaptonuria was the first described "inborn error of metabolism". This rare (<1 per 250.000 births) hereditary recessive disorder is characterized by triad of excretion of homogentisic acid in the urine, ochronosis (dark pigmentation of the connective tissues) and early onset arthritis. Blackish pigmentation of the cornea and ear cartilage, high incidence of heart disease (mitral and aortic valvulitis, calcification of the heart valves and myocardial infarction) have also been noted [4]. It results from absence of an enzyme, homogentisic acid oxidase. In Turkish alcaptonuric patients R225H and R 58fs HGO (homogentisate 1,2-dioxigenase) gene mutations are common [5]. However, mutation analysis could not be performed in our patients.

There is no specific and effective treatment for alkaptonuria. The treatment focuses upon these aspects: correction of the production of HGA and prevention of complications. For reduction of HGA excretion has been suggested treatment with vitamin C and protein restriction have been proposed [6-11]. It involves giving a low-protein diet with restriction of phenylalanine and thyrosine. The World Health Organization recommends a dietary protein intake of at least 1.4 g/kg/per day for all growing children [11]. However, this is not a very practical measure.

Our patients were consuming a diet with low protein. They living in Sivas, an eastern province of Turkey where socioeconomic conditions are unsatisfactory and consanguineous marriages are very high. Nutrition of patients was largely derived from leavened bread, cereals, vegetables and negligible amount of animal protein, which is characteristic of high-phytate fiber foods in Turkey. This finding demonstrated that our patients were showed normal growth and development and no major complications of the disease because of consuming a diet with low protein.

Ascorbic acid is given in the dose of 500 mg BID to reduce connective tissue damage. Presumably the ascorbic acid with its antioxidant property helps to retard the process of conversion of homogentisate to polymeric material that is deposited in cartilaginous tissues [10, 11]. Five-year-old boy was administered oral ascorbic acid (0.5 g/day) daily for the management of alkaptonuria.

Some clinical trials demonstrated that benefits of nitisinone. Nitisinone, a potent inhibitor 4-hydroxyphenyl pyruvate dioxygenase, dramatically reduces production and urinary excretion of HGA; however, the long-term efficacy and side effect of such therapy are unknown [2, 12, 13].

References

1. Prasad C, Galbraith PA. Sir Archibald Garrod and Alcaptonuria. Clin Genet 2005; 68: 199-203.
2. Phornphutkul C, Introne WJ, Perry MB, Bernardini I, Murphey MD, Fitzpatrick DL, Anderson PD, Huizing M, Anikster Y, Gerber LH, Gahl WA. Natural history of alkaptonuria. N Engl J Med 2002; 347: 2111-21.
3. Lorenzini S, Mannoni A, Selvi E. Alcaptonuria. N Engl J Med 2003; 348:1408.
4. Keller JM, Nercessian OA, Jaffe IA. New developments in ochronosis: review of the literature. Rheumatol Int 2005; 25: 81-5.
5. Uyguner O, Goicoechea de Jorge E, Cefle A, Baykal T, Kayserili H, Cefle K, Demirkol M, Yuksel-Apak M, Rodriguez de Córdoba S, Wollnik B. Molecular analyses of the HGO gene mutations in Turkish alkaptonuria patients suggest that the R58fs mutation originated from central Asia and was spread throughout Europe and Anatolia by human migrations. J Inherit Metab Dis 2003; 26: 17-23.
6. Verma SB. Early detection of alkaptonuria. Indian J Dermatol Venereol Leprol 2005; 71: 189-91.
7. Jeucken YM, Visser G, Jaarsma AS, van Spronsen FJ. A child with dark discoloration of urine. Ned Tijdschr Geneeskd 1999;143: 1641-3.
8. Morava E, Kosztolányi G, Engelke UF, Wevers RA. Reversal of clinical symptoms and radiographic abnormalities with protein restriction and ascorbic acid in alkaptonuria. Ann Clin Biochem 2003; 40: 108-11.
9. Forslind K, Wollheim FA, Akesson B, Rydholm U. Alkaptonuria and ochronosis in three siblings. Ascorbic acid treatment monitored by urinary HGA excretion. Clin Exp Rheumatol 1988; 6: 289-92.
10. Wolff JA, Barshop B, Nyhan WL, Leslie J, Seegmiller JE, Gruber H, Garst M, Winter S, Michals K, Matalon R. Effect of ascorbic acid in alkaptonuria alterations in benzoquinone acetic acid and an ontogenic effect in infancy. Pediatr Res 1989; 26: 140-4.
11. Mayatepek E, Kahas K, Anninos A, Müler E. Effect of ascorbic acid and low-protein diet in alkaptonuria. Eur J Pediatr 1998; 157: 867-8.
12. Suzuki Y, Oda K, Yoshikawa Y, Maeda Y, Suzuki T. A novel therapeutic trial of homogentisic aciduria in a murine model of alkaptonuria. J Hum Genet 1999; 44: 79-84.
13. Suwannarat P, O'Brien K, Perry MB, Sebring N, Bernardini I, Kaiser-Kupfer MI, Rubin BI, Tsilou E, Gerber LH, Gahl WA. Use of nitisinone in patients with alkaptonuria. Metabolism 2005; 54: 719-28.