Erciyes Med J 2012; 34(2): 88-90 • DOI: 10.5152/etd.2012.22

Alkaptonuria: a Presentation of Two Turkish Cases

Alkaptonüri: İki Türk Olgunun Sunumu

CASE REPORT
OLGU SUNUMU

Mustafa Kendirci[1], Nihal Hatipoğlu[2], Fatih Kardaş[1], Melike Nadide Sav[3]

ABSTRACT
ÖZET

Alkaptonuria is a rare, inherited metabolic disorder caused by a deficiency in homogentisic acid (HGA) oxygenase oxidase. HGA, an intermediary product in the metabolism of phenylalanine and tyrosine, cannot be further metabolised in cases of alkaptonuria. The metabolic defect causes a characteristic triad of homogentisic aciduria, ochronosis and arthritis. HGA is excreted in urine, turning dark brown or black upon oxygenation and alkalinisation. With complaints of black-colored urine without any other findings and increased urinary HGA excretion confirmed by gas chromatography-mass spectrometry, two cases, three-and ten-year-old boys, are presented and the relevant literature is discussed.

Alkaptonüri, homojgentisik asid (HGA) oksijenaz oksidaz eksikliğine bağlı olarak gelişen, genetik otozomal resesif olarak kalıtılan bir hastalıktır. geçişli ve metabolik bir hastalıktır. Olgularda Hastalarda fenilalanin ve tirozin metabolizmasının ara ürünü olan HGA metabolize olamaz olan HGA yıkılamaz ve hastalık sonuçta ve HGA birikimi vucütta birikir ile seyreder. Metabolik bozukluk sonucu hastalığın triadı olan homojgentisik asidüri, okronoz ve artrit oluşur. HGA, idrarla atılırken oksijenasyon ve alkalinizasyona bağlı olarak idrarı koyu kahverengi veya siyah renge çevirir. Bu yazıda Çalışmamızda idrar renginin siyahlaşması şikayeti ile başvuran ve Gaz Kromotografisi-Kütle Spektrometri ile idrarda yüksek HGA atılımı saptanan, 3 ve 10 yaşlarında, iki erkek olgu hasta sunuldu ve literatür gözden geçirildi.

Key words: Alkaptonuria, homogentisic acid

Anahtar kelimeler: Alkaptonüri, homogentisik asit

[1]Department of Pediatric Nutrition and Metabolism, Faculty of Medicine, Erciyes University, Kayseri, Turkey

[2]Department of Pediatric Endocrinology, Faculty of Medicine, Erciyes University, Kayseri, Turkey

[3]Department of Pediatrics, Faculty of Medicine, Erciyes University, Kayseri, Turkey

Submitted/Geliş Tarihi
15.06.2009

Accepted/Kabul Tarihi
30.03.2012

Correspondance/Yazışma
Dr. Fatih Kardaş,
Department of Pediatric Nutrition and Metabolism, Faculty of Medicine, Erciyes University, 38039 Kayseri, Turkey
Phone: +90 3524374937-25473
e.mail: fkardas@erciyes.edu.tr

Introduction

Alkaptonuria (AKU) is a rare metabolic disorder of phenylalanine catabolism that is inherited as an autosomal recessive trait (1). The incidence of alkaptonuria in Turkey and globally has not been reported yet. AKU is caused by a deficiency of in homogentisic acid (HGA) oxygenase oxidase in the phenylalanine/tyrosine catabolic pathway in the liver, kidney, prostate, small intestine and colon (2). The first sign of the disease in childhood is the typical black colour of the urine, which is due to high levels of oxidised HGA (3). The urine is a normal colour when passed, but rapidly darkens to black upon exposure to atmospheric oxygen or other oxidative conditions. This accumulation of oxidised HGA polymers in the connective tissue leads to ochronosis in early adulthood and causes degenerative arthritis in mid-life (4). This article reports two cases of AKU, aged three and ten years old, with the complaint of black-coloured urine at the time of diagnosis. Previously, HGA was identified by paper chromatography, but more recently the diagnosis has been performed by detecting increased levels by gas chromatography-mass spectrometry (GC-MS) (5, 6).

Case Reports

Case 1

A three-year-old boy was admitted to the clinic by his parents who were concerned about the changing colour of his urine (turning to black) since his birth. There was no consanguinity with his parents, family history of similar complaints or history of any drug intake in the recent past. His physical examination was normal. There was no joint pain and the X-rays of the hip, spine and knees were unremarkable. There was also nothing to suggest a cardiac problem as the electrocardiogram and the echocardiogram were normal. When a freshly voided urine sample was requested from the parents, it was black in colour. They said that it was normal in colour while the child was voiding, but it changed colour after about half an hour of standing. The reaction of the urine with sodium hydroxide was positive and increased HGA excretion (927.8 mmol/mol creatinine; N <2 mmol/mol creatinine) was detected by GC-MS (Figure 1).

Case 2

A ten-year-old boy of a non-consanguineous marriage was admitted to the clinic with a complaint of black-coloured urine. He was the third child of the family. There was no family history of similar complaints. His growth and developmental history were within normal ranges. He had been fed with only breast milk for the first four

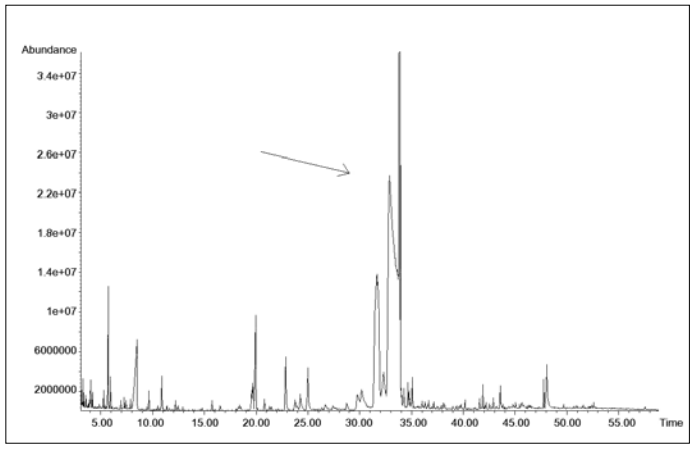

Figure 1. Homogentisic acid peak (arrow) detected by GC-SM in Case 1

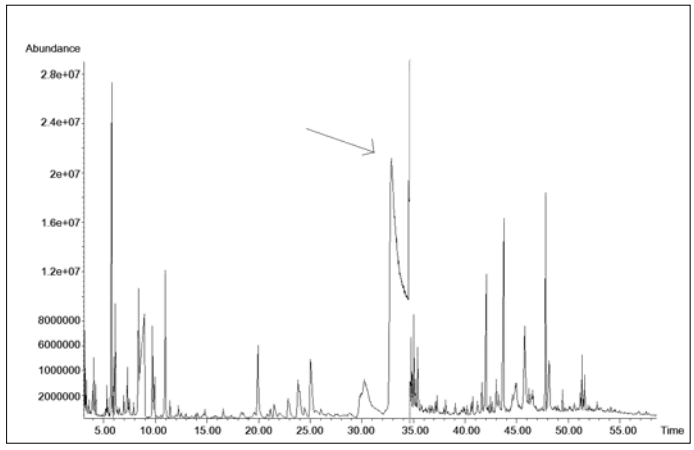

Figure 2. Homogentisic acid peak (arrow) detected by GC-SM in Case 2

months of life. The physical examination was normal. The findings of the cardiovascular system and the X-rays of the thoracolumbar spine, knees and hips were unremarkable. No pathological findings were observed on ophthalmological examination. Laboratory analyses included complete blood count, liver and renal function tests, serum levels of calcium, phosphate and magnesium, erythrocyte sedimentation rate and urine analysis and were within the normal ranges. The fresh urine of the child darkened within thirty minutes. The reaction with sodium hydroxide was positive. Urinary organic acid analysis by GC-MS revealed increased excretion of HGA (1825 mmol/mol creatinine; N: <2 mmol/mol creatinine) (Figure 2).

Discussion

As an inborn error of metabolism, AKU was the first human disease interpreted as a Mendelian trait by Garrod and Bateson at the beginning of the last century (7). It is a rare metabolic disorder of phenylalanine catabolism and is inherited as an autosomal recessive trait (1). It is caused by a deficiency in HGA oxygenase oxidase (HGO) which converts HGA to maleylacetoacetate in the phenylalanine/tyrosine catabolic pathway in the liver, kidney, prostate, small intestine and colon (2). The accumulation of HGA in bodily fluids leads to the characteristic symptoms (black urine, ochronosis and arthritis) of the disease (8). Patients may be homozygous or compound heterozygous for loss-of-function mutations in the HGO gene. More than 40 different mutations have been identified in a total of fewer than 100 unrelated patients from many different countries (9). No method for the detection of heterozygotes has been devised (1).

The disorder may be noted when a child's napkins turn dark over time, but it occasionally passes unnoticed until the patient presents in middle or late life with back pain due to spinal ochronotic spondylosis and the characteristic densely calcified intervertebral discs with relatively few other symptoms of degenerative arthritis. The typical radiographic appearances of ochronotic spondyloarthropathy are wafer-like calcifications in the intervertebral discs, with narrowing of disc spaces and osteoporotic rarefaction in the vertebral bodies (4). In contrast to rheumatoid arthritis, the small joints of the hands and feet are usually not affected, and ankylosing spondylitis, bamboo spine, annular ossification, syndesmophytes, erosion and fusion of sacroiliac joints do not occur (10).

The classic clinical triad of the disorder are 1) homogentisic aciduria which presents at birth (pathogonomic sign: urine blackens upon standing when oxidised or alkalinised), 2) gradual development of ochronosis, deposition of polymers of oxidised HGA in connective tissues leading to intensive eumelanin-like pigmentation of the skin, sclera, cartilage, etc. after the age of 20 to 30 years and 3) degenerative ochronotic arthropathies usually developing in the fourth decade of life (10). Alkaptonuric ochronosis rarely involves the cardiovascular system and the urinary tract (10, 11). An increased amount of HGA in the urine estimated by GC-MS confirms the diagnosis of the disorder (12, 13).

There is no effective treatment for AKU. Some studies have reported success with dietary protein restriction and using vitamin C and nitisinone therapies (14, 15) that have not been confirmed by others (16). Other agents such as vitamin B12, cortisone and phenylbutazone are without influence on the metabolic defect. Replacement of the missing enzyme is theoretically a therapeutic measure to consider, but this is not available at present (1).

We encountered two cases of AKU with complaints of black-coloured urine without any evidence of cardiovascular system, renal, eye or connective tissue involvement. The reaction of the urine with sodium hydroxide was positive and increased amounts of HGA excretion were determined by GC-MS in these cases, while other laboratory findings were normal.

Conclusion

Alkaptonuria is a rare metabolic disorder which causes black-coloured urine and multisystem complications in later ages. Early diagnosis is important to follow up the complications of this disease and further investigations are required to develop an effective treatment for AKU.

Acknowledgements
The present study was presented at the IXth National Nutrition and Metabolism Congress, 22-25 October 2007, İstanbul, Turkey.

Conflict of interest
No conflict of interest was declared by the authors.

Authors' contributions: Conceived and designed the study: MK, NH, FK, MNS. Examination and follow-up of the patient: MK, NH, FK, MNS. Wrote the paper: FK. All authors read and approved the final manuscript.

References

1. La Du BN. Alkaptonuria. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Editors. The Metabolic and Molecular Bases of Inherited Disease. New York: McGraw-Hill; 2001. p.2109-2120.
2. Fernández-Cañón JM, Peñalva MA. Molecular characterization of a gene encoding a homogentisate dioxygenase from aspergillus nidulans and idendification of its human and plant homologues. J Biol Chem 1995; 270(36): 21199-205. **[CrossRef]**
3. Pollak MR, Chou YH, Cerda JJ, Steinmann B, La Du BN, Seidman JG, et al. Homozygosity mapping of the gene for alkaptonuria to chromosome 3q2. Nature Genet 1993; 5(2): 201-4. **[CrossRef]**
4. Watts RW, Watts RA. Alkaptonuria: a 60-year follow-up. Rheumatology (Oxford) 2007; 46(2): 358-9. **[CrossRef]**
5. Bory C, Boulleu R, Chantin C, Mathleu M. Homogentisic acid determined in biological fluids by HPLC. Clin Chem 1989; 35(2): 321-2.
6. P Rinaldo, Organic acids, in: N. Blau, M. Duran, K.M. Gibson (Eds.), Laboratory Guide to the Methods in Biochemical Genetics, vol., Springer Verlag, Heidelberg, 2008, pp. 137-70. **[CrossRef]**
7. Garrod AE. The incidence of alkaptonuria: a study of chemical individuality. Lancet 1902; 2: 1616-20. **[CrossRef]**
8. Knox WE. Sir Archibald Garrod's inborn errors of metabolism. II. Alkaptonuria. Am J Hum Genet 1958; 10(2): 95-124.
9. Fernández-Cañón JM, Granadino B, Beltrán-Valero de Bernabé D, Renedo M, Fernández-Ruiz E, Peñalva MA, et al. The molecular basis of alkaptonuria. Nat Genet 1996; 14(1): 19-24. **[CrossRef]**
10. Fisher AA, Davis MW. Alkaptonuric ochronosis with aortic valve and joint replacements and femoral fracture: a case report and literature review. Clin Med Res 2004; 2(4): 209-15. **[CrossRef]**
11. Ffolkes LV, Brull D, Krywawych S, Hayward M, Hughes SE. Aortic stenosis in cardiovascular ochronosis. J Clin Pathol 2006; 60(1): 92-3. **[CrossRef]**
12. Seegmiller JE, Zannoni VG, Laster L, La Du BN. An enzymatic spectrophotometric method for the determination of homogentisic acid in the plasma and urine. J Biol Chem 1961; 236:774-7.
13. Hill A, Hoag GN, Zaleski WA. The investigation of aromatic acids in phenylketonuria, alkaptonuria and tyrosinosis using gas- liquid chromatography. Clin Chim Acta 1972; 37: 455-62. **[CrossRef]**
14. Morava E, Kosztolany 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(Pt 1): 108-11. **[CrossRef]**
15. Wolf JA, Barshop B, Nyhan WL, Leslie J, Seegmiller JE, Gruber H, et al. Effects of ascorbic acid in alkaptonuria: alterations in benzoquinone acetic acid and an ontogenic effect in infancy. Pediatr Res 1989; 26(2): 140-4. **[CrossRef]**
16. 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 1998; 6(3): 289-92.