Alkaptonuria: a Presentation of Two Turkish Cases

Alkaptonüri: İki Türk Olgunun Sunumu

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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 requested from the parents, it was black in colour. They said that it was normal in colour while the child was voiding.

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 years of life.

Key words: Alkaptonuria, homogentisic acid

Anahtar kelimeler: Alkaptonüri, homogentisik asit

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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 maleylacetacetae 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).

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, Istanbul, 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.
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