ALKAPTONURIA: CASE REPORT AND REVIEW OF THE LITERATURE

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Alkaptonuria (McKusick 203500) is a rare metabolic disease characterized by a triad of homogentisic aciduria, arthritis and ochronosis. It enjoys the historic distinction of being one of the first conditions in which mendelian recessive inheritance was proposed and is also one of the conditions in the charter of group of inborn errors of metabolism.[1] It is of interest to note that the disease was identified in 1500 BC in an ancient Egyptian mummy.[2] The manifestations are urine that turns dark on standing and alkalinization due to excretion of excessive amounts of homogentisic acid, large joint arthritis and black ochronotic pigmentation of cartilage and collagenous tissue. This disease is unusually frequent in Slovakia[3] and the Dominican Republic.[4]

More than 126 patients have been reported from Czechoslovakia,[5] 108 from Germany, and 90 from the United States. In countries of the Middle East, the disease was first reported from Lebanon in 1958[6] and from Sudan in 1965.[7] Two adult patients, one Saudi and one Yemeni, have also been reported from Saudi Arabia.[8,9] We report the first Saudi child with presymptomatic alkaptonuria, who was diagnosed and treated at King Faisal Specialist Hospital and Research Centre, and we discuss the clinical aspect and management of this condition with a review of the relevant literature.

Case Report

A 4-year-old boy of a first-degree consanguineous couple was noted by the parents to have darkening of the urine to an almost black color when it was left standing. He had a normal sibling and there were no other medical problems, in particular hemolytic anemia, in the family. Childhood growth and development were normal. Physical examination revealed a healthy child with normal growth parameters. In particular, there was no abnormal pigmentation of the sclera, conjunctiva, cornea and ear cartilage. Joint examinations were normal as well. The patient's urine appeared normal during voiding, however, it turned black on standing in room temperature (Figure 1). Regular laboratory investigations were normal and skeletal survey showed no degenerative changes. The urine gas chromatography/mass spectrometry (GC/MS) showed a massive amount of homogentisic acid. He was started on Vitamin C (0.5 g/bid). Currently, the patient is asymptomatic and is under follow-up every six months in the Outpatient Clinic. After screening the close and extended family members, no other cases were identified.

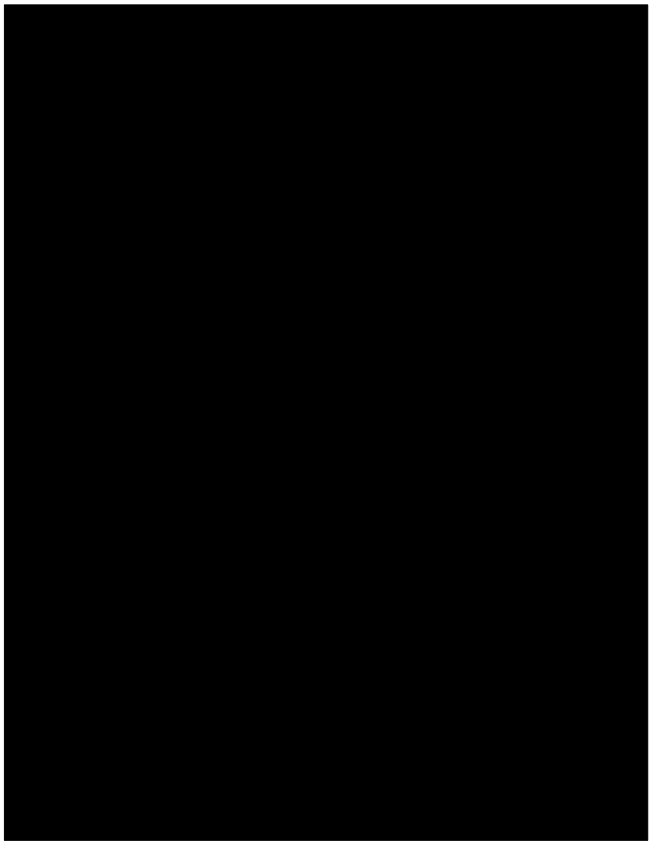

FIGURE 1. Left: fresh urine of the patient. Right: darkening of the urine to an almost black color on standing.

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Discussion

Alkaptonuria, or the excretion of urine which darkens on exposure to air, is an autosomal recessive disorder due to deficiency of homogentisic acid oxidase, an important enzyme in the catabolism of aromatic amino acids. It catalyzes the conversion of homogentisic acid to maleylacetoacetic, which is ultimately converted to fumaric and acetoacetic acid[10] (Figure 2).

The urine of an alkaptonuric individual usually appears normal when passed. However, it starts to darken upon standing. This is caused by oxidation and polymerization of the homogentisic acid, and it is enhanced with an alkaline pH. Therefore, an acidic urine may not become dark even after many hours of standing. This is one of the reasons why darkening of the urine may perhaps never be noted in an affected person, and the diagnosis may be delayed until adulthood, when arthritis or ochronosis occurs.

Homogentisic acid is a strong reducing agent that produces a positive reaction with Fehling or Benedict reagent, a feature that was also recognized in 1859.[11] The diagnosis is confirmed by measurement of homogentisic acid by enzymatic spectrophotometry,[12] or by using gas liquid chromatography.[13] The diagnosis could also be confirmed by the high-pressure liquid chromatography method for the quantitation of homogentisic acid and its derivative benzoquinone acetic acid.[14] Measurement of this product by this method is used for therapy monitoring. Excretion of homogentisic acid in the urine is usually massive—as much as 4 to 8 g of this compound is excreted daily in the urine,[15] and very little is found in the plasma.

Alkaptonuric patients are usually asymptomatic as children or young adults.[16-18] When they get older, pigmentation of the sclera or the cartilage of the ear start to appear. Pigmentation may be seen in the teeth,[19] buccal mucosa, and in the nails or the skin, giving these areas a dusty coloration. The widespread deposition of pigment in alkaptonuric patients is called ochronosis,[20,21] a term used to describe the darkening of tissues, which is due to a slow accumulation of the black polymer of homogentisic acid in the cartilage and other mesenchymal tissues.

Arthritis is the only disabling effect of this con dition, and occurs in almost all patients with advancing age.[22,23] The earliest symptoms are usually in the hips, spine and knees, the large weight-bearing joints. The arthritis has the clinical characteristics of rheumatoid arthritis, however, the radiological picture is of severe osteoarthritis. In contrast to osteoarthritis, the large joints at the hip and shoulder are most commonly involved, whereas the sacroiliac joint may be spared. The degenerative changes in the lumbar spine are quite characteristic, with narrowing of joint spaces and fusion of vertebral bodies, resulting in marked limitations of motion with ultimate ankylosis. Ochronotic arthropathy in the hips and the knees may be so severe as to require total joint arthroplasty.[24] The disease is more severe in men, although the incidence in the two sexes is equal.[25]

There is a high incidence of heart disease,[26] commonly due to mitral and aortic valvulitis. Secondary calcification of the aortic valve may be so severe as to necessitate urgent aortic valve replacement.[27] Ischemic heart disease with ultimate myocardial infarction is a common cause of death.

Genetically, alkaptonuria is inherited as an autosomal recessive trait.[26] Janocha et al.[28] demonstrated linkage to microsatellite markers from proximal 3q. Markers on that chromosome were selected for study because of previously demonstrated homology of synteny with mouse chromosome 16.[29] Independently, Pollak et al.[30] used homozygosity mapping to locate the alkaptonuric gene to 3 q 2 in a 16-cM region. Sucrase-isomaltase deficiency[31] and neonatal hyperparathyroidism[32] could be co-inherited with alkaptonuria. In 1996, Fernandez-Canon et al. cloned the gene for homogentisate 1,2 dioxygenase (HGD,EC 1.13.11.5), and they demonstrated that HGD harbors the mutation that co-segregates with the disease and provided biochemical evidence that at least one of these missense mutations is a loss of function mutation.[33]

Treatment of alkaptonuric patients is a challenge for a pediatrician. No treatment has been completely successful. Dietary restrictions on the intake of tyrosine and phenylalanine substantially reduced the excretion of homogentisic acid, however, the long-term compliance with this diet is the major drawback of this approach.[14] Homogentisic acid inhibits the growth of cultured human articular chondrocyte, and binds to connective tissue in rats.[34] Ascorbic acid prevents these effects. Wolff et al. treated two adults with high doses of ascorbic acid. The level of excretion of homogentisic acid did not change, whereas its derivative, benzoquinone acetic acid, completely disappeared from the urine.[14]

FIGURE 2. Pathway showing the defective homogentisic acid oxidase which catalyzes the conversion of homogentisic acid to maleylacetoacetic acid, causing the disease alkaptonuria.

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