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## Alkaptonuria in a middle-aged female

### Abstract

**Background:** Alkaptonuria (AKU) or ochronosis is a rare progressive degenerative arthropathy that results from deficiency of enzyme homogentisate 1,2 dioxygenase (HGD). The features include arthritis of the spine and in larger peripheral joints, with chondrocalcinosis. In this paper, we present a case of alkaptonuria in a 54 year old woman in Tehran, Iran.

**Case Presentation:** A 54 year old woman with pain and limitation of motion in hip and lumbar spine was admitted in Firoozgar Hospital, Tehran. The problem began about 12 years ago with a history of darkening of urine and discoloration of sclera and ears. In imaging studies, there were degenerative changes in spine. In urine examination, the darkening of urine after exposure to air or bicarbonate found. Alkaptonuria was confirmed by demonstrating an increased homogentisic acid (HGA) in urine. Her sister had back pain for a long period of time without response to therapy. She was subsequently diagnosed with alkaptonuria.

**Conclusion:** Alkaptonuria must be considered in the evaluation of low back pain of patients especially with having a positive family history and bluish discoloration of cartilage tissues.

**Keywords:** Alkaptonuria, Ochronosis, Degenerative arthropathy

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**A**lkaptonuria (AKU) is a rare autosomal recessive inherited disorder that causes a progressive degenerative arthropathy (1- 2). The disease usually begins in the fourth decade of life (1, 3). This rare disease affects 1 in 250,000 to 1 million people worldwide (1, 4). Alkaptonuria is more common in Slovakia with an incidence of about 1 in 19,000 people (1). Mutations in the HGD gene cause alkaptonuria. The HGD gene is necessary for the synthesis of homogentisate oxidase (5). This enzyme causes breaking of the phenylalanine and tyrosine, which are important for the structure of proteins. Mutations in the HGD gene impair the enzyme's activity in this process, resulting in the accumulation of homogentisic acid in various bodily tissues (5-7). Excess homogentisic acid and related compounds are deposited in connective tissue, which causes cartilage and skin to darken (6, 8-9). The accumulation of homogentisic acid causes cartilage destruction. Homogentisic acid is also excreted in urine which causes the urine to turn dark when exposed in the air (10). In this article, we present a case of alkaptonuria in a middle-aged woman in Tehran, Iran.

### Case Presentation

A 54 year old woman was admitted in Firouzgar Hospital, Tehran, Iran, in May 2010 for severe low back pain and limitation of motion. The problem began about 12 years ago and progress during this time and did not respond to drugs and other therapeutic modalities.

She had a history of discoloration of urine that changed to black after urination. She had positive family history of back pain in her sister for a long period of time without response to therapy. In physical examination, the vital sign was normal. In the head and neck examination, three angular pigmentation was seen in sclera and bluish discoloration of auricle found (figure 1, 2). The examination of chest and abdomen was normal. Morning stiffness was less than 10 minutes and back pain had mechanical characteristics.



**Figure 1. Pigmentation in the sclera**

In axial examination, there was no tenderness in spine but limitation of motion found in all plane of movements. The shober test was positive. The hip examination revealed some motional limitation in all directions particularly the left hip. Other peripheral joints were normal. There were no abnormal findings in the other examinations. In radiological studies, loss of intervertebral disc spaces was prominent and degenerative changes were found in hip joints (figure 3). Through urine examination, adding of bicarbonate to urine causes a change into black.

Concentration of homogentisic acid in urine was 3.85 mmol/L of creatinine and the concentration of homogentisic acid in plasma was 7.3 micrograms/ml.



**Figure 2: Bluish discoloration of auricle**



**Figure 3. X-ray of the lumbar spine of the patients**

### Discussion

In this article we present a patient with alkaptunuria that complained back and hip pain for more than 12 years without appropriate response to treatment. Some specific findings included discoloration of ear cartilage and triangular pigmentation of sclera. Excess homogentisic acid and related compounds are deposited in connective tissue, which causes cartilage and skin to darken (6, 8-9). Homogentisic acid is also excreted in urine, causes the urine turn dark when exposed to air (10). Features include arthritis of the spine and in larger peripheral joints which sometimes develop to chondrocalcinosis (10).

Clinically, the disease resembles ankylosing spondylitis, with progressive lumbar rigidity but morning stiffness and enthesitis that occurs predominantly in spondyloarthropathies are less common in alkaptunuria (11). The difference of this disease with spondyloarthropathies is very important because the second ones have inflammatory nature and can be managed with appropriate therapy including anti TNF medications but alkaptunuria is degenerative disease and do not have any known effective treatment. Flexion contractures of the knee sometimes occur with effusions (6, 10). Non-articular features of ochronosis include bluish discoloration of the ear pinnae, triangular pigmentation of the sclera, and pigmentation over the nose, axillae, and groin (5, 10). Prostatic calculi are also common in men, and cardiac murmurs sometimes occur due to deposition of pigment in cardiac valves (5-6, 12).

A specific enzymatic method permits quantitation of homogentisic acid in urine and blood. Meanwhile, in alkaptunuria, its plasma concentration increases approximately up to 6.6  $\mu\text{g/ml}$  and the levels of creatinine

goes up to 3.12 mM/ml in urine (5, 8). Effusions of the joints contain calcium pyrophosphate dehydrate (CPPD) crystals but without inflammation (1, 4). Multiple vacuum discs of the spine occur on roentgenograms. The spine shows ossification of the discs with narrowing, and collapse (5, 10). Chondrocalcinosis affects pubic symphysis, costal cartilage, ear helix and unusual dark pigmentation on the tympanic membrane (3, 8, 13).

The early roentgenographic appearance of the peripheral joints resembles osteoarthritis but with few osteophyte formation and more symmetric narrowing of joint space and linear or punctuate calcifications of joint space (5). The most prominent differences with crystal disorders are in lacking of acute arthritis attack and degenerative features of imaginary findings. There is no effective therapy for the underlying metabolic disorder (6). Positive family history and darkening of urine after alkalization and at least increasing level of HGA in urine confirm the diagnosis. Although, we did not find respiratory problems in our patient, various cases had been published in which dyspnea might develop as a result of the stiffening of cartilage in the chest wall (14).

In conclusion, Alkaptonuria must be considered in the evaluation of low back pain of patients particularly with positive family history and bluish discoloration of cartilage tissues.

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**Conflict of interest:** None

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