Case Report

Three cases of alkaptonuria in one family in Mazandaran Province, Iran

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Received: 12 Dec 2012
Revised: 27 Jan 2013
Accepted: 11 Feb 2013

Abstract

Background: Alkaptonuria is a rare genetic disease leading to the accumulation of homogentesic acid in joint and ear cartilage, sclera and some other tissues causing significant morbidity in these patients. In this paper, we report three cases of Alkaptonuria among the family or household members.

Case Presentation: A 51-year-old man with mechanical low back and knee pain was referred to Rheumatology Clinic of Babol University of Medical Sciences. The physical examination showed thoracic kyphosis and limitation of motion in thoraco-lumbar spine, severe knee osteoarthritis and blue-black discoloration of ear cartilages. There was intervertebral disc calcification in plain radiography, and mitral valve calcification in echocardiography. His urine sample was tested positive in Benedict's test. The diagnosis was confirmed by qualitative assessment of homogentesic acid (HGA) that was highly positive. In addition, we found two more cases of Alkaptonuria in his family.

Conclusion: Although alkaptonuria is a rare disease, but it may be found in cluster among the family members.

Keywords: Alkaptonuria, Cluster, Iran

Caspian J Intern Med 2013; 4(2): 677-680

Alkaptonuria is an inborn error of metabolism with the excessive accumulation of homogentesic acid polymers in connective tissues (1, 2). It has autosomal recessive inheritance, and the location of mutated gene is on the chromosome 3q21-q23 (3). The prevalence of AKU was reported 1/250,000- 1/1,000,000 in 2005 (4). Today, it has increased to 1/100,000- 1/250,000, but in some countries like Slovakia the frequency is by far higher (1/19,000) (1, 3). The disease is seen equal in males and females, but the symptoms begin earlier and more severe in males (5). Normally, homogentesic acid (HGA) is the product of the catabolism of phenylalanine and tyrosin (4, 6, 7). Homogentisate 1, 2 dioxigenase, or homogentesic acid oxidase (HGAO), the enzyme that is found in the liver and kidney, prostate and intestine and probably in the joints is responsible for the conversion of HGA to maleylacetoacetic acid (1, 2, 6, 7).

The mutation of this enzyme leads to the accumulation of HGA in tissues, and then converts to benzoquinone acetic acid (BQA) (2). Polymerization of BQA produces pigments with melanin color that is toxic for the connective tissues (2). It also passes in the urine and after exposure to air or oxygenation and alkalinisation, changes to black urine (1, 2, 6). The other clinical features of AKU are blue-black discoloration of ear, sclera, even in nose and cheeks, severe degenerative arthropathy in the knees, hips, shoulder joints and spine with kyphosis, calcification of intervertebral discs and the features of canal stenosis, calcification of cardiac valves and coronary vessels, renal, prostate and salivary gland stones, tendon rupture, hearing and voice problems, renal and liver cyst (1, 2, 5, 6, 8, 9).

The diagnosis is based on the clinical features, change of urine color in standing or with adding Naoh 10%, Agno3 or Benedict test (1).

This will be confirmed with quantitative measurement of HGA level in the urine by gas chromatography-mass spectrophotometry (2, 6). Currently there is no cure for this disease. Conservative treatment for arthropaties, restriction of dietary proteins and vitamin C supplementation have been advised. The only drug that may help is nitisinon.

This drug inhibits p-hydroxy phenyl pyruvate dioxigenase, and decreases HGA production (9). In this srudy we present three cases of alkaptonuria in a family.

Case presentation

A 51-year-old man was referred to Rheumatology Clinic of Babol University of Medical Sciences because of low back pain. Also, he was complaining of chronic mechanical knee pain. The physical examination showed signs of severe knee osteoarthritis and thoracic kyphosis and limitation of motion in thoraco-lumbar spine. There was blue- black discoloration of both ears (figure 1).

His urine color turned to dark brown after few minutes and his underwear always had black stains, but he has never complained about it before. Plain radiography of the knees and lumbar spine showed osteoarthritis and calcification of intervertebral discs (figure 2).

Decreased patelo-femoral joint space, osteophyte formation and loose bodies around the knee joints is shown in figure 3. His urine produced positive Benedict's test (figure 4).

The other laboratory tests were normal. The ultrasonography of kidneys and prostate was normal but the echocardiography showed mitral valve calcification (figure 5). Because of ST & T changes in electrocardiography, coronary angiography was down. There was only significant stenosis in diagonal branch. The diagnosis was confirmed by qualitative assessment of HGA by CENTOGENE GmbH in Rostock, Germany, that was highly positive (roughly 850 mmol/mol creatinin with normal range <2).

In the family examination, his elder sister had arthropathy like our patient with positive Benedict's test in urine. The younger brother was 27 years old and he had only positive urine test with no other signs. His father passed away many years ago.

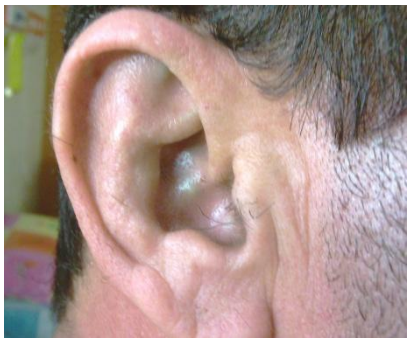

Figure 1. Blue-Black discoloration of ear cartilage

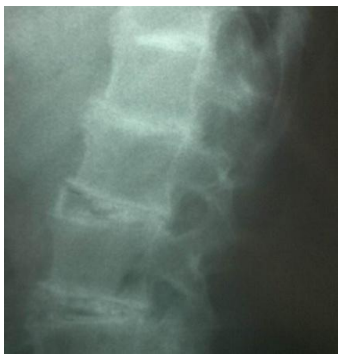

Figure 2. X-ray of lumbar spine showing intervertebral calcification

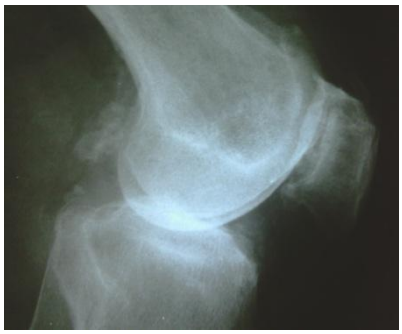

Figure 3. X-ray of knee (lateral view) showing severe osteoarthritis and loose bodies

Figure 4. Benedict's test in normal person (left) and the patient (right)

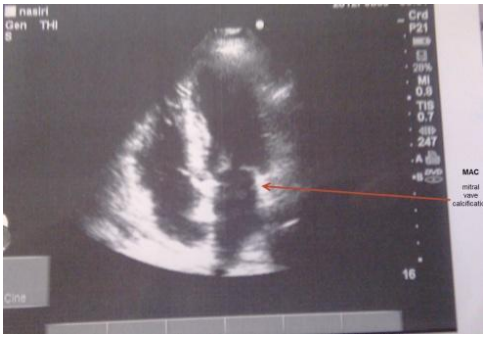

Figure 5. Trans thoracic echocardiography of the patient showing calcification of mitral valve

Discussion

Alkaptonuria is an autosomal recessive disorder. It is more prevalent in some countries like Slovakia. In a study that has been published in 2011 in Slovakia, 208 cases of AKU have been reported (9). This is also confirmed in the latest map published by AKU society. In this map, the total number of AKU cases in Europe was 429, United states 87, Canada 23, Australia 14, Asia 75, and in the Middle East 94. Most cases reported in the Middle East were from Jordan with 54 cases. But there was no case from Iran in the above mentioned reports. However, we found three relevant articles in the literature review. The first one was from Tabriz city in 2002. They reported 3 cases of AKU after discectomy surgery (10). The other one was diagnosed during the operation of a pathologic hip fracture in a 54-year-old woman (11). The third one, with similar clinical features like this patient was reported in 2012 (12).

In the present case, severe low back pain and knee pain, and thoracic kyphosis and the question mark posture were the reasons of the diagnosis of ankylosing spondylitis in the beginning. However, the long history of black urine color, blue black discoloration of ears, severe osteoarthritis, calcification of intervertebral discs, calcification of mitral valve and positive Benedict's test in the patient and this family, suggested Alkaptonuria. Indeed, our patient fulfilled the diagnostic criteria of this disease including homogentisicaciduria (urine darkens on standing or with alkalinization), gradual development of ochronosis (melanin like pigmentation of sclera, cartilages and skin) and degenerative ochronotic arthropathy (6). The diagnosis is confirmed with the measurement of urinary homogentisic and by gas chromatography-mass spectrophotometry (2, 6). This will be done for this family and their relatives. Given that there is no cure for these patients, screening can prevent the birth of new cases. In summary, although alkaptonuria is a rare disease, however, it may be found in cluster among the family members.

Acknowledgments

This work was presented by one of us (A.G) during the Sixth International Workshop on AKU, Piešťany, Slovakia, 1-2 November 2012. We would like to thank Dr Leona Wagner and Dr Nick Sireau from the AKU Society, and Dr Lakshminarayan Ranganath fron Royal Liverpool University Hospital for the discussions and inputs during the preparation of this article.

Conflict of Interest: There was no conflict of interest.

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