

CASE REPORT

Neglected Alkaptonuric Patient Presenting with Steppage Gait

Babak Mirzashahi, MD; Abbas Tafakhori, MD; Arvin Najafi, MD; Mahmoud Farzan, MD

*Research performed at Joint Reconstruction Research Center, Orthopedic Department, Imam Khomeini Complex Hospital, Tehran, Iran**Received: 8 November 2015**Accepted: 28 November 2015***Abstract**

Even though intervertebral disc degeneration can be found in the natural course of alkaptonuria, detection of the disease by black disc color change in a patient without any other presentation of alkaptonuria is an exceptionally rare condition. We have reported a very rare case of alkaptonuria presented with low back pain and steppage gait in a 51-year-old male with a complaint of chronic low-back pain and steppage gait who was operated on for prolapsed lumbar disc herniation. Intraoperatively his lumbar disc was discovered to be black. The alkaptonuria diagnosis was considered after histopathological examination of the black disc material and elevated urinary concentration of homogentisic acid confirmed the diagnosis. To our knowledge, this presentation has not been reported previously in literature.

Keywords: Alkaptonuria, Black disc material, Herniation, Lumbar disc, Ochronosis, Steppage gait

Introduction

Alkaptonuria (AKU) is a very rare hereditary metabolic disorder with an incidence of nearly 1 in 1 million individuals (1, 2). This disorder is inherited as an autosomal recessive characteristic and defined by an absence of the enzyme homogentisate 1,2-dioxygenase (HGD). This enzyme has a role in the aromatic amino acids metabolic pathway in the kidneys and the liver, and further excretion of homogentisic acid (HGA) in urine or is aggregated in the tissues (3, 4). The polymerization and oxidation of homogentisic acid causes black coloration of urine and the connective tissues where HGA is deposited (3, 4).

The first presentation of this disease in childhood is the typical black color of the urine. Individuals with alkaptonuria usually have dark urine or urine that turns dark on standing or when exposed to an alkaline agent. However, darkening may not occur for several hours after voiding, and many individuals may never observe any abnormal color of their urine. Thus, fresh urine may look normal in alkaptonuric patients. Ochronosis is a condition that may be observed on the skin, nails, teeth and the patient's buccal mucosa pigmentation. In ochronosis, the HGA pigment is deposited with a high affinity in the hyaline cartilage tissues of large joints and sclera and intervertebral discs (3). Severe degenerative disorders happen in the joints and spinal column, predominantly

in the thoracic and lumbar regions usually between third and fifth decades of life (5). Although disc degeneration is prevalent in ochronosis, gait disorders and intervertebral disk herniation are unusual, and there are only a few cases that have been treated by surgery and published in the literature.

Case report

A 51-year-old man with a six-month history of progressive weakness of both lower limbs with right side dominance and chronic nonspecific low back pain was referred to our orthopedic outpatient clinic. He had no other considerable feature in his past medical history and his family history was normal: his mother, father and brothers were in a good health. Neurological examination revealed impaired right foot and toe dorsiflexion. Lower limb muscle forces were 4/5 both in the distal and proximal components bilaterally and positive Lasegue's sign was detected. Steppage gait was obvious during his walking and patellar reflex on his right side was diminished. Electromyogram and nerve conduction studies showed active bilateral radiculopathy with right side dominance in L2-L5 levels. Anteroposterior and lateral radiographs of the spine revealed significant degenerative changes and narrowed intervertebral spaces [Figure 1]. Sagittal and axial sections of lumbar magnetic resonance imaging showed multilevel disk degeneration and disk bulging at L4-L5 and L2-L3

Corresponding Author: Babak Mirzashahi, Imam Khomeini Hospital, Tehran University of Medical Sciences, Bagherkhan St, Tehran, Iran
Email: babakmirzashahi54@gmail.com



THE ONLINE VERSION OF THIS ARTICLE
ABJS.MUMS.AC.IR



Figure 1. The black color change of involved lumbar disk can be observed.

and protrusion at L2-L3. Lateral recess stenosis at L2-L5 with Modic changes in L5-S1 was seen [Figure 2]. His routine laboratory examinations did not show any notable point. The electromyogram of the patient showed chronic radiculopathy of the L3, L4, and L5 nerve roots. He filled out the SF36 (quality of life) and Visual Analogue Scale (VAS) before the surgery and Oswestry Disability Index (ODI) was measured by the surgeon. He was operated on for prolapsed disc herniation. There was no abnormality in skin, muscles or ligaments during surgery. Laminectomy, partial facetectomy and discectomy were executed in L2-L3 and L3-L4 and L4-L5 levels. After the annulus was cut, the



Figure 2. Lateral radiography of our patient shows significant degenerative changes and narrowed intervertebral spaces.

nucleus pulposus was removed from the disc spaces which were black in color [Figure 3]. The microscopic findings were melanin-like pigmentations in the cytoplasm of the chondrocytes. After the surgery the patient was re-examined for alkaptonuria. In the end gas chromatography/mass spectrometry of the urine proved the AKU diagnosis in the patient and revealed a high intensity peak of HGA. The postoperative follow up was acceptable, the patient was free from steppage gait and impaired dorsiflexion after surgery and his low back pain was gradually alleviated. He was treated and discharged with oral ascorbic acid (1 g per day) after 10 days hospitalizations. Physiotherapy and dietary restrictions were also recommended. One month after surgery the patient was reevaluated and had recovered full motor function and complained of mild low back pain. The postoperative questionnaires (SF36, VAS, ODI) were again filled out and they all showed significant improvement in the patient's condition.

Discussion

Alkaptonuria is an autosomal recessive metabolic disorder with an incidence of nearly 1 in 1 million individuals that is defined by an absence of the enzyme homogentisate 1,2-dioxygenase (HGD) (1, 2). It is characterized by accumulation of homogentisic acid (HGA) in the tissues. The HGA pigment is deposited with high affinity in the hyaline cartilage tissues of large joints and the sclera and intervertebral disc. Disc generation happens usually between the third to fifth decades of ages. Alkaptonuric ochronosis is characterized by slow accumulation of HGA and its oxidation products (e.g., benzoquinone acetic acid) in connective tissues causing bluish-black pigmentation of the involved body areas. The initial presentation of ochronosis is a trivial pigmentation of ears or sclera in young adults, but only a minor group of



Figure 3. Magnetic resonance imaging of our patients shows multilevel disk degeneration and disk bulging at L4-L5 and L2-L3 and protrusion at L2-L3.

patients with alkaptonuria develop ochronotic arthropathy (6). It is believed that the human hepatobiliary system produces enough HGD to metabolize over 1.5 kg of HGA daily (7). Consequently, a loss of more than 99% of the enzyme activity is needed in order to display alkaptonuria symptoms. Variability in residual HGD enzymatic activity may elucidate the absence of a strong association between phenotype and genotype (8). Additionally, in the skin and cartilage of such patients homogentisic acid polyphenoloxidase catalyzes the overall oxidation and polymerization of HGA to a "ochronotic-like" pigment that harms and blackens connective tissues. Discolorations of sclera or nasal and ear cartilages have been reported as the primary presentations of alkaptonuric patients with low back and leg pain (9, 10). While Choudhury et al. and Kahveci et al. have reported that ochronosis patients with low back pain and sciatica without any pigmentation changes at primary visits (11, 12). But MRI and CT scan findings of all of these patients had similar findings including narrowing of disc spaces, disk protrusion, osteophytes, and calcification.

Some authors believe that in patients with alkaptonuria who have no ochronotic signs and symptoms, in addition to HGD homogentisic acid, polyphenol oxidase deficiency might be found (13). Ochronotic arthritis is a common sign of longstanding alkaptonuria. The musculoskeletal presentations of alkaptonuria are likely to be noted first in the spine. The most distinctive spine abnormality of this disease is extensive calcification of the intervertebral discs. Degenerative changes may be presented along the entire spine; however, the most noticeable involvement is in the lumbar area. In the some features of clinical and radiological characteristics, ochronosis may look like hemochromatosis, ankylosing spondylitis (AS), and idiopathic chondrocalcinosis. The first pathology to be noted in differential diagnosis is AS, which has similar clinical findings. Ankylosing spondylitis shows sacroiliac and facet

joint arthropathy in radiographs without calcification in intervertebral discs. There is no localized skin, sclera and cartilage tissues discoloration. The classic radiological sign of ochronosis is intervertebral disc calcifications, which may be infrequently found in hemochromatosis and idiopathic chondrocalcinosis. The retrospective diagnosis of alkaptonuria by a "black" disc material obtained during discectomy is exceptionally rare (6, 14-16). Homogentisic acid levels are increased in urine samples of all these patients. Also, diffuse degenerative changes and disc calcifications are the characteristic radiological findings. Surgical results are acceptable in all of these cases. Discoloration of the skin, ear and darkening of the urine were detected in our patient's long term follow up re-examination. Patients with alkaptonuria may benefit from supportive therapy, but at present there is no established effective treatment or prophylaxis regime. If necessary, corrective operative processes like discectomy or decompression of the spinal cord have been helpful in this patients (17, 18). Early diagnosis and suitable treatment of the complications is important in order to decrease the morbidity, particularly in patients with no other signs of alkaptonuria. Therefore, orthopedic surgeons should be aware of metabolic disorders such as alkaptonuria in the differential diagnosis of degenerative disc disease.

Babak Mirzashahi MD
Arvin Najafi MD
Mahmoud Farzan MD
Joint Research Center, Imam Khomeini Hospital, Tehran
University of Medical Sciences, Tehran, Iran

Abbas Tafakhori MD
Tehran University of Medical Sciences, Tehran, Iran

References

1. Millea TP, Segal LS, Liss RG, Stauffer ES. Spine fracture in ochronosis. Report of a case. *Clin Orthop Relat Res.* 1992; 28(1):208-11.
2. Gaines JJ Jr. The pathology of alkaptonuric ochronosis. *Hum Pathol.* 1989; 20(1):40-6.
3. Feild JR, Higley GB Sr, Desaussure RL Jr. Ochronosis with ruptured lumbar disc: case report. *J Neurosurg.* 1963; 20(4):348-51.
4. McCollum DE, Odom GL. Alkaptonuria, ochronosis, and low-back pain. A case report. *J Bone Joint Surg Am.* 1965; 47(7):1389-92.
5. Koh KB, Low EH, Ch'ng SL, Zakiah I. A case of alkaptonuria with root canal stenosis. *Singapore Med J.* 1994; 35(1):106-7.
6. Laskar FH, Sargison KD. Ochronotic arthropathy. A review with four case reports. *J Bone Joint Surg Br.* 1970; 52(4):653-66.
7. La Du BN. Alkaptonuria. In: Scriver CR, editor. *The metabolic and molecular basis of inherited disease.* 8th ed. New York: McGraw-Hill; 2001. P. 2109-23.
8. Vilboux T, Kayser M, Introne W, Suwannarat P, Bernardini I, Fischer R, et al. Mutation spectrum of homogentisic acid oxidase (HGD) in alkaptonuria. *Hum Mutat.* 2009; 30(12):1611-9.
9. Farzannia A, Shokouhi G, Hadidchi S. Alkaptonuria and lumbar disc herniation. Report of three cases. *J Neurosurg.* 2003; 98(1 Suppl):87-9.
10. Gürkanlar D, Daneyemez M, Solmaz I, Temiz C. Ochronosis and lumbar disc herniation. *Acta Neurochir (Wien).* 2006; 148(8):891-4.
11. Choudhury R, Rajamani SS, Rajshekhar V. A case of ochronosis: MRI of the lumbar spine. *Neuroradiol-*

- ogy. 2000; 42(12):905-7.
12. Kahveci R, Ergüngör MF, Günaydin A, Temiz A. Alkaptonuric patient presenting with "black" disc: a case report. *Acta Orthop Traumatol Turc.* 2013; 47(2):134-8.
 13. Zannoni VG, Lomtevas N, Goldfinger S. Oxidation of homogentisic acid to ochronotic pigment in connective tissue. *Biochim Biophys Acta.* 1969; 177(1):94-105.
 14. Choudhury R, Rajamani SS, Rajshekhar V. A case of ochronosis: MRI of the lumbar spine. *Neuroradiology.* 2000; 42(12):905-7.
 15. Farzannia A, Shokouhi G, Hadidchi S. Alkaptonuria and lumbar disc herniation. Report of three cases. *J Neurosurg.* 2003; 98(1 Suppl):87-9.
 16. Gürkanlar D, Daneyemez M, Solmaz I, Temiz C. Ochronosis and lumbar disc herniation. *Acta Neurochir (Wien).* 2006; 148(8):891-4.
 17. Reddy DR, Prasad VS. Alkaptonuria presenting as lumbar disc prolapse: case report and review of literature. *Spinal Cord.* 1998; 36(7):523-4.
 18. Emel E, Karagöz F, Aydın IH, Hacısalihoglu S, Seyithanoğlu MH. Alkaptonuria with lumbar disc herniation: a report of two cases. *Spine (Phila Pa 1976).* 2000; 25(16):2141-4.