ISSN 1220-8841 (Print)
ISSN 2344-4959 (Online)

ROMANIAN
NEUROSURGERY

Vol. XXXVII | No. 3 September 2023

From low back pain to ochronosis. A case of late diagnosed alkaptonuria

Turkan Turgay,
Erdal Yayla,
Murat Baloglu

DOI: 10.33962/roneuro-2023-059

Romanian Neurosurgery (2023) XXXVII (3): pp. 328-332
DOI: 10.33962/roneuro-2023-059
www.journals.lapub.co.uk/index.php/roneurosurgery

From low back pain to ochronosis. A case of late diagnosed alkaptonuria

Turkan Turgay, Erdal Yayla, Murat Baloglu

[1] SANKO University, Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Gaziantep, TURKEY
[2] SANKO University, Faculty of Medicine, Department of Neurosurgery, Gaziantep, TURKEY
[3] Eskisehir City Hospital, Department of Neurosurgery, Eskisehir, TURKEY

Keywords
Alkaptonuria, homogentisate 1,2, dioxygenase, ochronosis, low back pain

ABSTRACT

Background: Alkaptonuria is a rare metabolic autosomal recessive disorder. Its aetiology involves homogentisate 1,2 dioxygenase (HGD) deficiency resulting in homogentisic acid accumulation in the connective tissues (ochronosis). The classic triad of the disease is: i) homogentisic aciduria, ii) bluish-black pigmentation in tissues such as the sclera, cornea, cartilage and skin, and iii) degenerative arthropathy usually in the fourth decade of life.

Case: In this case report, we present a 41-year-old man with diffuse musculoskeletal pain and additional clinical features in tissues such as the ear and urinary tract who was diagnosed late (>30 years). He was diagnosed with alkaptonuria based on clinical findings and elevated urinary homogentisic acid levels.

Conclusion: This case report underscores the need for early diagnosis of alkaptonuria, which can help in managing symptoms and improving the quality of life of patients. Further research is needed to develop more targeted therapies for alkaptonuria, which can help slow down the progression of joint degeneration and improve overall patient.

INTRODUCTION

Alkaptonuria, also known as ochronosis, is a rare metabolic autosomal recessive disorder. The disease is characterized by accumulation of homogentisic acid in collagenous tissues such as cartilage. This is due to a deficiency in the HGD 1,2 enzyme involved in phenylalanine and tyrosine metabolism. In addition to bluish-black cartilage discoloration, progressive ochronotic arthropathy is observed. This may lead to calcification of tendons, ligaments and intervertebral discs, degeneration of large joints, inflammation and bone resorption. The diagnosis is based on clinical history, urinary homogentisic acid level, histopathologic and genetic examination. Although treatment options are limited, early diagnosis can prevent joint and spinal deformities and organ dysfunction. We aimed to present a patient with a delayed

Corresponding author:
Murat Baloglu

Eskişehir City Hospital, Department of Neurosurgery, Turkey

apopitozis@gmail.com

ISSN online 2344-4959
© Romanian Society of Neurosurgery

First published
September 2023 by
London Academic Publishing
www.lapub.co.uk

diagnosis of alkaptonuria with musculoskeletal, ear and urinary findings.

41-year-old male, university graduate, suffering from severe low back pain for the past three months was admitted to our clinic. It was learned that his complaints had been intermittent for 8 years. He described morning stiffness for 15-20 minutes and pain that subsided with rest. He had a 5-year history of a lumbar discectomy and right renal calculi. Family history revealed persistent dark urine and suspicion of rheumatologic disease in all siblings.

Clinical evaluation revealed a bluish coloration of the ear cartilages (Figure 1). Physical examination revealed decreased lumbar lordosis, thoracic kyphoscoliosis, limited and painful lumbar spine movements in all directions. The patient's lumbar Schober measurement was 2.0 cm.

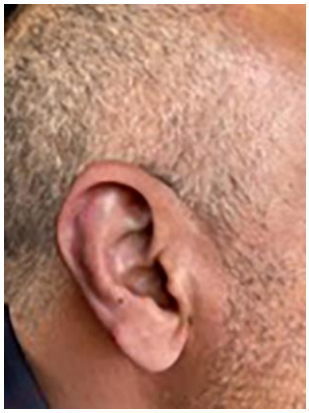

Figure 1. Bluish discoloration of the cartilage of the external ear.

Lumbar vertebral radiography showed intervertebral disc calcification, vacuum phenomenon, degenerative changes and a stone in the lower pole of the right kidney. Pelvic radiography showed bilateral sacroiliac joint narrowing, increased sclerosis and similar degenerative changes (Figure 2).

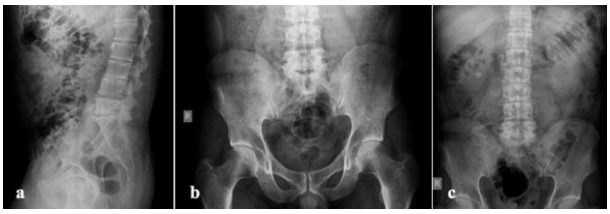

Figure 2. Narrowing of intervertebral disc spaces, disc calcifications, vacuum phenomenon, osteophytic degenerative changes on lumbar vertebral radiography, narrowing of sacroiliac and hip joint space, increased sclerosis on pelvic radiography.

Lumbar magnetic resonance imaging (MRI) showed mild distortion of the lumbar axis, kyphotic appearance at the thoracolumbar level, degenerative changes in the lumbar vertebrae with marginal osteophytes, Schmorl's nodules, narrowing of the disc spaces, disc protrusions compressing the talar sac, and degenerative changes in the facet joints (Figure 3). At the L4-L5 level, there was a left laminectomy operation defect and a paracentral protrusion at this level. This compressed the tibial sac and left L5 nerve root. When the patient's past imaging studies were examined, lower abdominal computed tomography showed prostatic calcification. The patient's urine turned dark brown when left to stand (Figure 4).

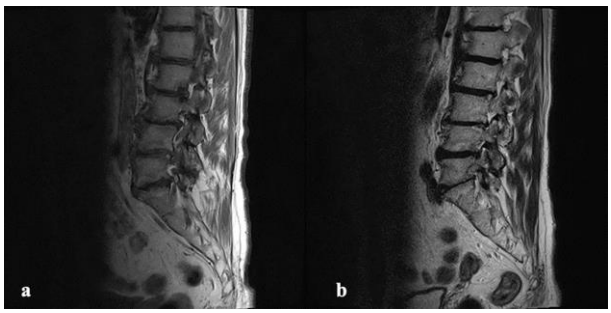

Figure 3. T1 and T2 weighted sagittal lumbar MRI image

Figure 4. Patient's dark brown urine at 0 and 18 hours.

A homozygous c.175delA/p.Ser59AlafsTer52 mutation was detected in the exons of the HGD gene of the patient in genetic analysis performed at an external center. Family screening was performed and it was found that his brother had a homozygous mutation and his sister had a heterozygous mutation. The patient was informed about alkaptonuria. Protein-free diets were started. He was referred to ophthalmology, cardiology, nephrology and urology for control and follow-up.The patient re-

applied to our clinic 6 months later with right knee pain. Physical examination revealed prepatellar swelling and patellofemoral crepitation. Right knee MRI revealed thinning cartilage and osteonecrosis (grade 4 chondromalacia patella), the largest being 5 mm in size in the subchondral bone of the patella joint (Figure 5).

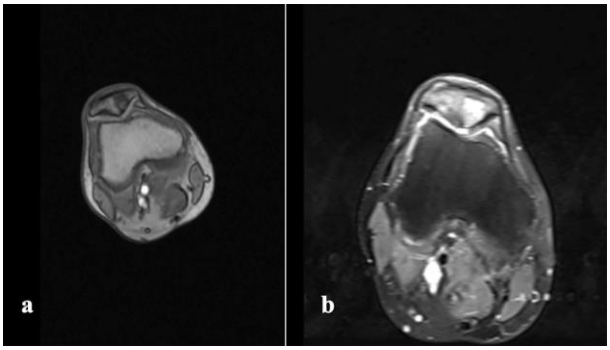

Figure 5. T1 and T2 weighted axial patellofemoral MRI image of the patient.

Characteristic clinical and radiologic findings suggested a possible diagnosis of alkaptonuria. The patient was started on 1 g/day vitamin C, analgesics, and nonsteroidal anti-inflammatory drugs. The patient was enrolled in a physical therapy program.

Discussion

The strength of this case is that it reflects the ability to classify a rare disease with a global prevalence of 1:100,000-250,000 (1) with possible suspicious and seemingly independent symptoms and signs. In addition, the patient underwent family screening with genetic examination after clinical diagnosis. In this way, the diagnosis of alkaptonuria was confirmed with a differential diagnosis of rheumatologic disease. Early treatment options were offered to his siblings.

The pathophysiology of alkaptonuria involves a deficiency in the enzyme homogentisate 1,2-dioxygenase. This enzyme deficiency leads to the accumulation of homogentisic acid in the body, which accumulates and deposits in bones and cartilage. This accumulation can lead to arthritis in affected joints and also cause a condition known as ochronosis, where the skin and other tissues darken 1.

As seen in our case, alkaptonuria is mostly asymptomatic in childhood and diagnosis is often delayed. Early diagnosis is key to preventing joint and spinal deformities and organ dysfunction. Many patients are also misdiagnosed with osteoarthritis. Differential diagnosis of ochronosis from diseases that cause disc calcification in the spine such as spondylosis, ankylosing spondylitis, pseudogout, hemochromatosis, amyloidosis and hypervitaminosis D should be made. Other features of alkaptonuria include aortic stenosis, vascular calcifications and a dark urine appearance due to HGA in the urine. Molecular genetic testing is not the gold standard for alkaptonuria diagnosis, as some polymorphisms may not cause the disease. Therefore, measurement of urinary HGA remains the classic diagnostic approach.

Patients are often not aware of the disease because of delayed referrals, misdiagnoses, and lack of awareness. However, when signs and symptoms reappeared later in life, the disease cannot be ignored. Genetic testing can provide the patient and their family members with disease information and help them make more informed medical and personal decisions.

There is currently no gold standard treatment for alkaptonuria. The development of disease sequelae can limit the available treatment options for alkaptonuria, including physical therapy, surgery, and analgesics. Nevertheless, dietary interventions may be effective in reducing phenylalanine and tyrosine intake that leads to homogentisic acid buildup within the body. By doing so, adverse effects associated with alkaptonuria could potentially be minimized through implementation of such measures. Nitisinone inhibits 4-hydroxyphenylpyruvate, the enzyme responsible for HGA production, and is currently approved for the treatment of hereditary tyrosinemia type 1. Studies have suggested that nitisinone may also be effective in reducing HGA levels in alkaptonuria patients. In several studies, nitisinone reduced urine and blood HGA levels by 95 percent 2. On the other hand, some argue that nitisinone may have potential benefits in the treatment of arthritis associated with alkaptonuria.

Although nitisinone did not show a significant improvement in a randomized clinical trial by Barconi et al (hip range of motion and other measures of musculoskeletal function), it is possible that different dosages or treatment regimens may yield better results 3. Treatment includes a low protein diet, ascorbic acid and lifestyle changes.

Dietary restriction of tyrosine and phenylalanine cannot reverse arthropathy, but may prevent clinical and radiologic progression. Ascorbic acid, which inhibits the enzyme catalyzing the oxidation of HGA to the polymer with collagen affinity, is given. However, its efficacy for ochronosis has not been proven 4. Therefore, although some treatments exist for alkaptonuria, more research is needed to develop effective therapies to manage the condition's joint-related complications.

Laura Groseanu et al. 5 initially diagnosed spondyloarthropathy; ankylosing spondylitis in a 55-year-old male patient with diffuse calcifications, who had onset of joint problems at an early age, morning stiffness, back and lower back pain, gradually increasing limitation of motion in the hip. However, intervertebral disc calcifications, history of kidney stones, aortic stenosis, pigmentation of the sclera, ear cartilage and hands suggested a late diagnosis of alkaptonuria.

Taşkıran et al., on the other hand, ordered urinalysis with a prediagnosis of HGA deficiency in a 71-year-old male patient who was incidentally observed to have blue pigments in the nose, cheeks and ears on routine physical examination, and who was diagnosed with hand arthrosis, dorsal kyphosis and bilateral hip prosthesis surgery due to early osteoarthritis 15 years ago on detailed physical examination and history, and made a diagnosis of delayed diagnosed alkaptonuria 6.

In a study including 58 patients with alkaptonuria, it was shown that only 12 (21%) of the patients were diagnosed before the age of 1 year. The remaining 32 patients (55%) were diagnosed because of dark urine, 26 patients (45%) were diagnosed because of chronic joint pain, and it was found that low back pain started before the age of 40 in 33 of 35 patients (94%) over the age of 40 7. As in our case, narrowing of the disc space, disc calcifications and disc fusion were observed at an early age. Although alkaptonuria shows spinal involvement similar to the clinical features of ankylosing spondylitis, kyphosis, loss of height and limitation in lumbar flexion, peripheral joint effusions, damage to the vertebrae and large joints differ 8. In the disease, joint symptoms typically begin in the third or fourth decade of life and progress until chronic pain leads to knee, hip or shoulder replacement; on average, this occurs at age 55 7.

Other manifestations include aortic or mitral valve calcification or insufficiency and sometimes aortic dilatation; kidney stones, prostate stones and hypothyroidism. Osteoarthritis, ankylosing spondylitis, Paget's disease, acute porphyria, valvular heart disease, rheumatoid arthritis, and melanosarcoma should be considered in the differential diagnosis. Although alkaptonuria does not seem to affect life expectancy, it has serious negative effects on quality of life. Complications include kidney, salivary gland, gallbladder and prostate stones, tendon and ligament tears, osteopenia and fractures, aortic valve calcification and stenosis, and amyloidosis 9.

Conclusions

As a result, the diagnosis and treatment of patients with alkaptonuric ochronosis, a rare inherited disorder, is highly complex. Early diagnosis is the key to the successful treatment of alkaptonuria. There is currently no effective treatment for the disease. In order to detect the disease as early as possible in the community, screening and genetic counseling should be carried out. A multidisciplinary approach aimed at improving quality of life and reducing morbidity should be the priority in the treatment of alkaptonuria patients.

References

1. Mistry JB, Bukhari M, Taylor AM. Alkaptonuria. Rare Dis. 2013;1:e27475.
2. Teke Kisa P, Eroglu Erkmen S, Bahceci H, et al. Efficacy of Phenylalanine- and Tyrosine-Restricted Diet in Alkaptonuria Patients on Nitisinone Treatment: Case Series and Review of Literature. Ann Nutr Metab. 2022;78(1):48-60.
3. Braconi D, Laschi M, Taylor AM, et al. Proteomic and redox-proteomic evaluation of homogentisic acid and ascorbic acid effects on human articular chondrocytes. J Cell Biochem 2010;111:922–32.
4. Rudebeck M, Scott C, Sireau N, Ranganath L. A patient survey on the impact of alkaptonuria symptoms as perceived by the patients and their experiences of receiving diagnosis and care. JIMD Rep. 2020;53(1):71-79.
5. Groseanu, Laura et al. A late and difficult diagnosis of ochronosis. J Med Life. 2010;3:(4):437-43.
6. Taşkıran E, Taş MY, Hışmi B, İnce FD, Ekmekçi S, Solakoğlu et al. A late diagnosis of alkaptonuria in an elderly patient. Eur Geriatr Med. 2017;8 (2):178-180.
7. Phornphutkul, Chanika et al. Natural history of alkaptonuria. N Engl J Med. 2002;347(26):2111-21.

8. Khan AH, Afroze B, Majid H, Zaidi Y, Jamil A, Jafri L. Musculoskeletal manifestations in Alkaptonuria: A cross-sectional study. Medicine. 2021;100(51):e28241.

9. Keller JM, Macaulay W, Nercessian OA, Jaffe IA. New developments in ochronosis: review of the literature. Rheumatol Int. 2005;25(2):81-85.