Case Report
Open Access
CrossMark

Alkaptonuria, a rare cause of early arthrosis in weight bearing joints – case report and review of literature

Abstract

Alkaptonuria is a rare autosomal recessive disorder caused by deficiency in homogentisate 1,2-dioxygenase, which leads to a tissue accumulation of homogentisic acid (HGA). HGA irreversibly deposits in connective tissues, which leads to degeneration of the articular cartilage, leaving these tissues with dark pigmentation, known as ochronosis.

Alkaptonuria typically presents with a triad of homogentisic aciduria, ochronosis and ochronotic arthropathy during the third and fourth decade of life. The ochronotic arthropathy is the most impactful complication in the quality of life, even though it virtually impacts every system.

There is no effective treatment, so intervention is based on symptoms, maintaining function and pain control while the inevitable deterioration of weightbearing joints progresses. Almost all patients are submitted to arthroplasties of the knee and/or hip. Soon there might be a way to prevent complications, has there are ongoing phase 3 studies to approve a drug that blocks the formation of HGA.

Volume 7 Issue 1 - 2022

Filipe Ermida,[1] Xénia Verraest,[1] Sandra Assunção,[1] Sofia Moreira,[1] André Ribeiro,[1] Ana Sofia Costa,[2] Rafaela Evangelista,[2] Eduardo Mendes,[2] Jorge Laíns[1,3]

[1]Centro de Medicina de Reabilitação da Região Centro, Rovisco Pais, Tocha, Portugal
[2]Centro Hospitalar Tondela, Viseu, Portugal
[3]Faculdade de Medicina, Universidade de Coimbra, Portugal

Correspondence: Filipe Ermida, Centro de Medicina de Reabilitação da Região Centro, Rovisco Pais, Rua da Fonte Quente, Tocha, Portugal, 3060-586, Tel +351967615853, Email filipecdneves@gmail.com

Received: January 25, 2022 | **Published:** February 10, 2022

Abbreviations: HGA, homogentisic acid; HGD, homogentisate1,2-dioxygenase; MRC, Medical Research Council

Introduction

Alkaptonuria is an autosomal recessive metabolic disorder, caused by a defect in the enzyme homogentisate1,2-dioxygenase (HGD) and it's characterised by increased circulation, and consequently accumulation, of homogentisic acid (HGA).[1–7] The mutated gene is localized in 3q21-23.[1,2,6]

It's a disorder with an incidence that varies between 1:250 000 and 1:1.000 000 people worldwide, without an ethnic prevalence,[1] although some regions of Slovakia and Dominican Republic have reported incidence of 1:19 000.[6]

Even though the low prevalence of this disease, it is recognised has one of the first pathologies, in which the mendelian model of autosomal recessive inheritance was proposed,[3,4,6,8,9] and in 1977, the presence of Alkaptonuria was identified in an Egyptian mummy named "Harwa", dated 1,500 BC.[10]

HGA is mostly excreted in urine, which, if left exposed to air, oxidises giving it a black colour, a condition that can be manifested from birth.[6,9,11]

However, part of the HGA is irreversibly deposited in the connective tissues,[3,4,6,9,12] and although the pathophysiological mechanism hasn't been completely clarified[5,6] it leads to the degeneration of the proteoglycan matrix of the articular cartilage, giving it the characteristic black pigmentation to these tissues.[3–6,9,12]

Alkaptonuria and ochronosis are not synonymous. Alkaptonuria is only one of the different causes of ochronosis.[9,13] The term ochronosis refers to the deposition of dark/ochre coloured pigments in connective tissues and may result from other exogenous causes such as hydroquinones, phenol, resorcinol and antimalarial drugs.[9,13–15]

Clinical case description

The clinical case in question concerns J.M., a 62-year-old Caucasian male patient, retired, having worked in construction until he was 49 years old. He was active and practised recreational physical exercise regularly until the age of 44, the age at which he developed effort-related knee and lower back pain.

In 2003 he was diagnosed with a narrowed lumbar canal, with a clinical presentation of low back pain irradiating to the lower limbs, for which he underwent surgical intervention on the lumbar spine. The surgery was interrupted after dark pigmentation of the ligaments and bone surfaces was found. A biopsy was performed for anatomopathological analysis which revealed degenerative arthropathy related to ochronosis (alkaptonuria).

In July 2019, due to complaints of right knee pain, combined with limited range of motion and imaging evidence of gonarthrosis, he underwent a total arthroplasty of the right knee. No complications were reported during or after surgery. After a rehabilitation programme, he reported functional gains and pain relief.

In February 2021, due to complaints of knee pain and functional limitation, now in the left knee and with imaging evidence of gonarthrosis, he underwent a total arthroplasty of the left knee, which was performed without complications. During the postoperative period, he suffered pulmonary embolism, which was addressed, and a complete recovery was obtained. He was prescribed an oral anticoagulant and no embolic complications were reported since.

The patient also had a personal history of renal colic, hypothyroidism, and an appendectomy during childhood. He reported that his urine changed from its usual yellowish colour to a dark colour when left exposed to the open air, which was confirmed during hospitalisation.

The patient followed the rehabilitation plan after the second total knee arthroplasty. He continued the follow up in the orthopedics department, where in May 2021, reported limited gait due to pain in the left hip, which radiated to the groin, a pain that prevented him from walking more than 100 metres straight. He walked using a crutch and had slight hip circumduction of the left leg.

On physical examination of the left knee, there was a scar on the anterior aspect, resulting from the most recent arthroplasty. The scar was clean, non-adherent and black in colour (ochronosis) (Figure 1). There was swelling and slight flushing around the joint. In knee flexion, he was able to achieve 5º to 110º of range of movement, both passive and active, and with muscular strength grade 4 on the Medical Research Council (MRC) scale.

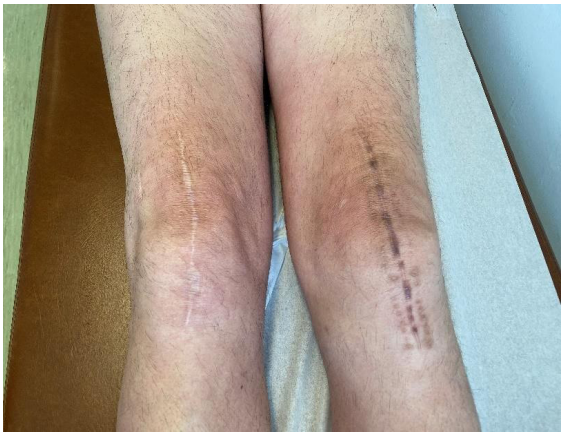

Figure 1 Scar pigmentation of the knees.

Likewise, the right knee presented a scar on the anterior aspect, derived from the arthroplasty of 2019. The scar was clean, non-adherent and light in colour (Figure 1). There was no sign of inflammation. The passive and active ranges of motion were 0º to 120º and muscle strength was grade 5 on the MRC.

The contrast between the colour of the two scars should be highlighted, as the white scar has developed for 2 years, while the more recent scar, which has only been developing for about 6 months, has a darker tone, which is in line with the accumulation of homogentisic acid in the connective tissue.

The left hip was painful when weight-bearing. He passively completed 80º of hip flexion, 20º of external rotation and 5º of internal rotation, all movements limited by pain.

He also reported pain on the right hip when weight-bearing, although to a lesser degree. On the right hip, he passively managed 90º of hip flexion, 30º of external rotation and 20º of internal rotation, also limited by pain.

An X-ray of the hip revealed advanced bilateral osteoarthrosis, classifying both hip joints as grade 3 according to Tonnis' classification (Figure 2).

A total hip arthroplasty on the left was proposed and accepted, during which the presence of ochronotic osteoarthropathy was confirmed, with dark staining of the cartilage and articular capsule, as well as of the surrounding ligaments (Figures 3–5).

Bone and cartilaginous tissue samples were collected for further histological analysis which confirmed synovitis of cartilaginous debris with yellowish-brown pigments compatible with the diagnosis of alkaptonuria.

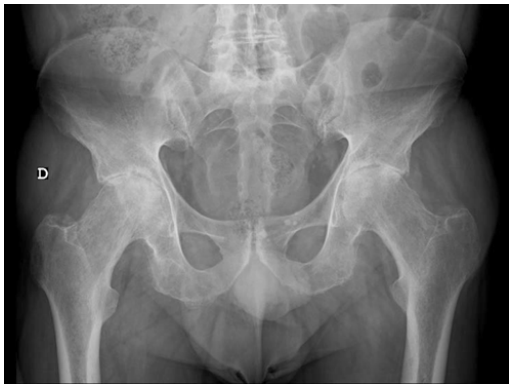

Figure 2 Pre-arthroplasty hip X-ray.

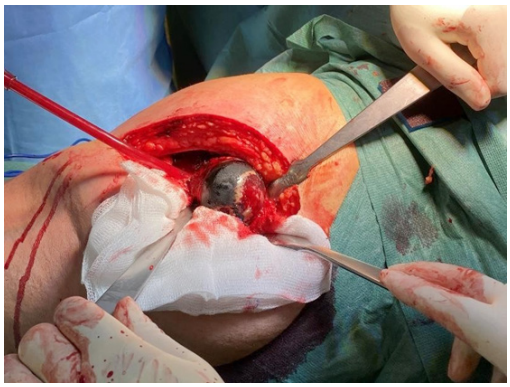

Figure 3 Removal of the femoral head.

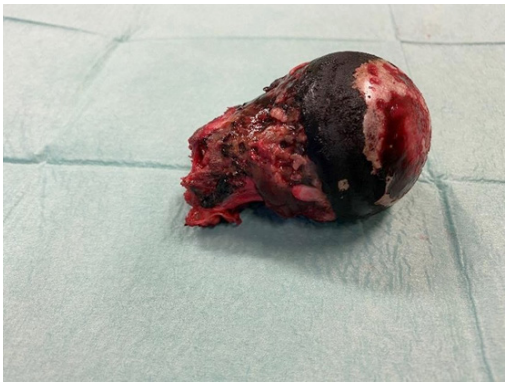

Figure 4 Femoral head and neck.

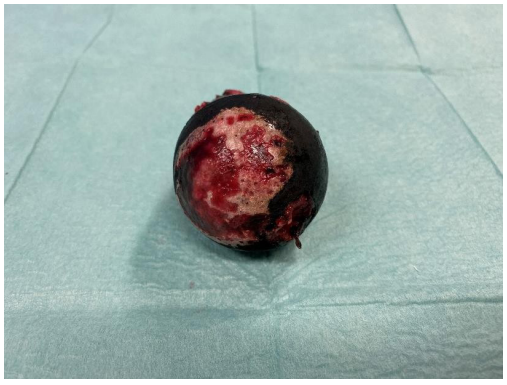

Figure 5 Articular face of the femoral head.

Upon reassessment one month after the surgery, the pain in the left hip had subsided, and he was not taking analgesics. He walked with

Citation: Ermida F, Verraest X, Assunção S, et al. Alkaptonuria, a rare cause of early arthrosis in weight bearing joints – case report and review of literature. *Int Phys Med Rehab J.* 2022;7(1):14–17. DOI: 10.15406/ipmrj.2022.07.00296

the support of two crutches because of pain in the right hip, which became more evident after the left hip arthroplasty. He performed 90º of active flexion of the left hip and managed 20º of passive internal and external rotations of the hip pain-free. No signs of hip prosthesis loosening were found in the control radiographic study (Figure 6).

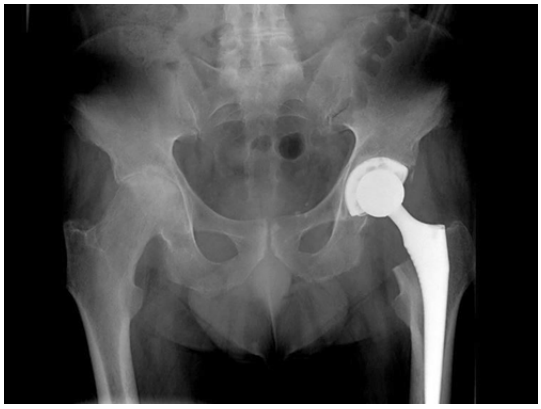

Figure 6 Post-arthroplasty hip X-ray.

Discussion

Classically, alkaptonuria presents with the triad of homogentisic aciduria, ochronosis and ochronotic osteoarthropathy, symptoms that generally manifest during the third and fourth decades of life.[3,4,6,11,16,17] Given the systemic involvement, cardiovascular, musculoskeletal, ophthalmic, cutaneous, respiratory and urinary tract manifestations may occur.[3,4,9,14,18,19]

Among the complications with potential health risk, we find cardiac ochronosis, which generally affects the aortic valve, resulting in aortic stenosis. More rarely it may affect the mitral valve and the coronary arteries.[3,4,6,20] This process of valvular ochronosis is typically detectable in the 6th decade of life.[3,4,6,21] It is thought that HGA accumulation is associated with oxidative stress at the cellular level, resulting in a chronic inflammatory state with subsequent calcium deposition.[16,20,22] However, the incidence of atherosclerosis and coronary artery disease in patients with Alkaptonuria seems to be similar to the incidence in the general population.[23]

HGA may precipitate and lead to renal and prostatic calculi,[3,4,9,24,25] usually detected as findings at routine examinations[26] between the 5th and 6th decades of life,[27] as many of the presentations are asymptomatic.[26] However, it may also progress to kidney failure requiring kidney transplantation.[25]

Finally, the ochronotic osteoarthropathy discussed in the present clinical case, resulting from the deposition of HGA in hyaline articular cartilage,[3,4,9,11,19] is one of the most characteristic presentations of Alkaptonuria, being part of the already mentioned triad of presentation.[11,16,17] It usually appears between the 3rd and 4th decades of life,[3,4] mainly affecting large weight-bearing joints such as the spine, hip and knee. The knee joint being the most impaired, followed by the hip,[28,29] with chronic progression until the eventual need for total joint arthroplasty,[6,28,29] around the 5th decade of life.[5,6]

The remaining tissues affected by Alkaptonuria-derived ochronosis are not associated with pathology, and their impact is mainly aesthetic.[3,4]

Diagnosis can be determined by HGA dosage in 24-hour urine samples and can also be complemented by genetic testing of the patient and family.[4,5,14,29–31]

Until recently, it was thought that no progression-modifying treatment for the disease existed.[6,12,19,29,30] Some studies have proposed that high doses of Vitamin D or N-acetyl- cysteine, could reduce the formation of homogentisic acid, but further investigation has not found evidence to justify their recommendation.[3,4,6,12,29]

However, recent studies have shown Nitisinone, a herbicide that inhibits the enzyme 4-hydroxyphenylpyruvate dioxygenase, responsible for the conversion of 4-hydroxyphenylpyruvate into HGA,[3,4,6,7,31] to be effective, not only in reducing urinary excretion of homogentisic acid,[31] but also in the development of ochronosis and other clinical signs, indicating a delay in disease progression.[7,32,33] Phase 3 studies are ongoing, with preliminary results indicating this drug as a promising candidate for the first specific therapeutic agent for Alkaptonuria.[7,32,33] A Nitisinone dose of 10 mg daily was shown to be safe and well tolerated, effective in slowing the progression of the disease, in a randomised controlled, double-blind, multicentre, international clinical trial, which followed the progression of the disease over 4 years, (SONIA 2).[33]

Alkaptonuria does not affect the average life expectancy,[11] but has a great impact on morbidity, particularly that resulting from the associated ochronotic arthropathy.[34]

The long-term results of total joint arthroplasty are favourable, and as such it is an acceptable option in the treatment of ochronotic arthropathy[6,19,35] and with implant lifetime comparable to cases of intervention for primary osteoarthrosis.[19,35]

A search in Pubmed, Cochrane and Medline with the mesh terms *"alkaptonuria" and "pulmonary embolism"* as well as *"alkaptonuria" and "embolism"* was performed, without finding any article reporting an episode of pulmonary embolism in a patient with alkaptonuria, which leads us to admit that these two conditions may not be directly associated.

Acknowledgments

None.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

None.

References

1. Vilboux T, Kayser M, Introne W, et al. Mutation spectrum of homogentisic acid oxidase (HGD) in alkaptonuria. *Hum Mutat*. 2009;30(12):1611–9.
2. Janocha S, Wolz W, Srsen S, et al. The human gene for alkaptonuria (AKU) maps to chromosome 3q. *Genomics*. 1994;19(1):5–8.
3. Phornphutkul C, Introne WJ, Perry MB, et al. Natural history of alkaptonuria. *N Engl J Med*. 2002;347(26):2111–2121.
4. Ranganath LR, Cox TF. Natural history of alkaptonuria revisited: analyses based on scoring systems. *J Inherit Metab Dis*. 2011;34(6):1141–1151.
5. Doganavsargil B, Pehlivanoglu B, Bicer EK, et al. Black joint and synovia: Histopathological evaluation of degenerative joint disease due to Ochronosis. *Pathol Res Pract*. 2015;211(6):470–477.
6. Gil JA, Wawrzynski J, Waryasz GR. Orthopedic Manifestations of Ochronosis: Pathophysiology, Presentation, Diagnosis, and Management. *Am J Med*. 2016;129(5):536.

7. Milan AM, Hughes AT, Davison AS, et al. Quantification of the flux of tyrosine pathway metabolites during nitisinone treatment of Alkaptonuria. *Sci Rep*. 2019;9(1):10024.
8. Garrod AE. The incidence of alkaptonuria: a study in chemical individuality. *Mol Med*. 1996;2(3):274–282.
9. Bluefarb SM. Alkaptonuria and ochronosis. *Q Bull Northwest Univ Med Sch*. 1958;32(2):101–105.
10. Stenn FF, Milgram JW, Lee SL, et al. Biochemical identification of homogentisic acid pigment in an ochronotic egyptian mummy. Science. 1977;197(4303):566–568.
11. Mistry JB, Bukhari M, Taylor AM. Alkaptonuria. *Rare Dis*. 2013;1:e27475.
12. Tinti L, Spreafico A, Braconi D, et al. Evaluation of antioxidant drugs for the treatment of ochronotic alkaptonuria in an in vitro human cell model. *J Cell Physiol*. 2010;225(1):84–91.
13. Zimmermann KG, Adolphsen P, Lenz H, et al. Alkaptonuria and ochronosis. *Dtsch Med Wochenschr*. 1972;97(7):242–244.
14. Albers SE, Brozena SJ, Glass LF, et al. Alkaptonuria and ochronosis: case report and review. *J Am Acad Dermatol*. 1992;27(4):609–614.
15. Keller JM, Macaulay W, Nercessian OA, et al. New developments in ochronosis: review of the literature. *Rheumatol Int*. 2005;25(2):81–85.
16. Braconi D, Millucci L, Bernardini G, et al. Oxidative stress and mechanisms of ochronosis in alkaptonuria. *Free Radic Biol Med*. 2015;88:70–80.
17. Detenbeck LC, Young HH, Underdahl LO. Ochronotic arthropathy. *Arch Surg*. 1970;100(2):215–219.
18. Gaines JJ Jr. The pathology of alkaptonuric ochronosis. *Hum Pathol*. 1989;20(1):40–46.
19. Karaoğlu S, Karaaslan F, Mermerkaya MU. Long-term result of arthroplasty in the treatment of a case of ochronotic arthropathy. *Acta Orthop Traumatol Turc*. 2016;50(5):584–586.
20. Gottschalk BH, Blankenstein J, Guo L. Ochronosis of Mitral Valve and Coronary Arteries. *Ann Thorac Surg*. 2018;106(1):e19–e20.
21. Hannoush H, Introne WJ, Chen MY, et al. Aortic stenosis and vascular calcifications in alkaptonuria. Mol Genet Metab. 2012;105(2):198–202.
22. Raina S, Mahesh DM, Kaushal SS, et al. Alkaptonuria and intramedullary calcification. *J Assoc Physicians India*. 2008;56:552–555.
23. Pettit SJ, Fisher M, Gallagher JA, Ranganath LR. Cardiovascular manifestations of Alkaptonuria. *J Inherit Metab Dis*. 2011;34(6):1177–1181.
24. Wolff F, Biaou I, Koopmansch C, et al. Renal and prostate stones composition in alkaptonuria: a case report. *Clin Nephrol*. 2015;84(6):339–342.
25. Introne WJ, Phornphutkul C, Bernardini I, et al. Exacerbation of the ochronosis of alkaptonuria due to renal insufficiency and improvement after renal transplantation. *Mol Genet Metab*. 2002;77(1-2):136–142.
26. Sali G, Thomas A, Kumar G, et al. Extensive prostatic calculi in alkaptonuria: An unusual manifestation of rare disease. *Asian J Urol*. 2015;2(3):179–181.
27. Sakthivel S, Zatkova A, Nemethova M, et al. Mutation screening of the HGD gene identifies a novel alkaptonuria mutation with significant founder effect and high prevalence. *Ann Hum Genet*. 2014;78(3):155–164.
28. Ozmanevra R, Güran O, Karatosun V, et al. Total knee arthroplasty in ochronosis: a case report and critical review of the literature. *Eklem Hastalik Cerrahisi*. 2013;24(3):169–172.
29. Couto A, Sá Rodrigues A, Oliveira P, et al. Ochronotic arthropathy-a rare clinical case. *Oxf Med Case Reports*. 2018;2018(9):069.
30. Introne WJ, Perry M, Chen M. Alkaptonuria. In: Adam MP, Ardinger HH, Pagon RA, editors. GeneReviews. Seattle (WA): University of Washington, Seattle; 1993–2021.
31. Ranganath LR, Milan AM, Hughes AT, et al. Suitability Of Nitisinone In Alkaptonuria 1 (SONIA 1): an international, multicentre, randomised, open-label, no-treatment controlled, parallel-group, dose-response study to investigate the effect of once daily nitisinone on 24-h urinary homogentisic acid excretion in patients with alkaptonuria after 4 weeks of treatment. *Ann Rheum Dis*. 2016;75(2):362–367.
32. Ranganath LR, Khedr M, Milan AM, et al. Nitisinone arrests ochronosis and decreases rate of progression of Alkaptonuria: Evaluation of the effect of nitisinone in the United Kingdom National Alkaptonuria Centre. *Mol Genet Metab*. 2018;125(1-2):127–134.
33. Ranganath LR, Psarelli EE, Arnoux JB, et al. Efficacy and safety of once-daily nitisinone for patients with alkaptonuria (SONIA 2): an international, multicentre, open-label, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2020;8(9):762–772.
34. Ranganath L, Taylor AM, Shenkin A, et al. Identification of alkaptonuria in the general population: a United Kingdom experience describing the challenges, possible solutions and persistent barriers. *J Inherit Metab Dis*. 2011;34(3):723–730.
35. Spencer JM, Gibbons CL, Sharp RJ, et al. Arthroplasty for ochronotic arthritis: no failure of 11 replacements in 3 patients followed 6-12 years. *Acta Orthop Scand*. 2004;75(3):355–358.

Citation: Ermida F, Verraest X, Assunção S, et al. Alkaptonuria, a rare cause of early arthrosis in weight bearing joints – case report and review of literature. *Int Phys Med Rehab J*. 2022;7(1):14–17. DOI: 10.15406/ipmrj.2022.07.00296