Hip and knee replacement in patients with ochronosis: Clinical experience and literature review

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Abstract

Patients with alkaptonuria can present ochronotic degenerative arthropathy due to the accumulation of pigments in the cartilages. Ochronotic arthropathy initially affects the spine, then there is the involvement of the other large joints, with greater frequency of the knees. In this article we will present two patients with alkaptonuria who have been effectively treated with knee and hip replacement, comparing our experience with what is available in the literature.

Introduction

Alkaptonuria is a rare autosomal recessive disorder of metabolism and has an estimated prevalence ranging from 1:200,000 to 1:1,000,000 live births worldwide, although an increased prevalence of disease of approximately 1 in 19,000 has been found in the Dominican Republic and within the Piestany region in Slovakia.[1] It is characterized by homogentisic acid (HGA) deposition in connective tissue as a result of a homogentisic 1,2-dioxygenase (gene onchromosome 3) deficiency, an enzyme that converts homogentisic acid (HGA) to maleylacetoacetic acid in the tyrosine degradation pathway and involved in the catabolism of phenylalanine.[2] In some cases the acid deposits in collagen-rich connective tissues. These deposits form plaques in the tissue that lead to the characteristic color of this disease, such as the dark color of the sclera,[3] ear and nose cartilage. The deposits can make the connective tissues rigid and usually lead to joint degeneration in the axial and appendicular skeleton by the fourth decade of life, termed "ochronotic arthropathy",[1] particularly hyaline cartilage and intervertebral discs and moreover it can determine,[4] even if rarely, the rupture of the tendons like the Achilles tendon as reported by Baca *et al*, Jiang *et al* and Wu *et al*.[5-7] Initially Alkaptonuria could manifest itself with a darkening colour of urine due to the presence of homogentisic acid.[8] The disease can also present the involvement of other systems, such as the cardiovascular system with valvulopathies and rarely coronary artery disease, as reported by Couto *et al*., Cetinus *et al*. and Planinc *et al*. So there are three major features in this disease: presence of HGA in the urine, ochronosis (presence of bluish-black pigmentation in connective tissue) and arthritis of the spine and larger joints.[9-11] The diagnosis of alkaptonuria may be confirmed by quantifying homogentisic acid in urine.[12] Differential diagnosis of this pathology is important from others that may involve full joints, such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis and Paget's disease, soft tissue disease, or bone tumor.[13-16] There is no specific treatment for alkaptonuria, other than a radical treatment such as liver transplantation,[1] currently therapies are symptomatic and make use of local heat, physiotherapy, analgesics and external support.[17] There is currently a molecule, nitisinone, that appears to slow down the progression of the disease and arrest the progression of combined ocular and ear ochronosis,[18] but at the same time causes an increase in tyrosine which can cause eye and skin keratopathy, so it may be necessary to combine an adequate diet.[19] There are many cases of hip and knee replacement in literature and in few cases the patient underwent replacement of both hips and knees.[20-21] Demir reported a case of a 70-year-old-man with four total joint replacement arthroplasties with good results.[22]

Clinical experience

In our clinical experience we have analyzed the data belonging to two patients.

Case Report #1

The first patient of age 72, male, presenting himself with pain in the spine and within articulations started at a young age. This patient had already been treated with drugs and articulatory injections with lack of response or benefits. He consequently decided to consult an Orthopedic clinic that redirected him to a Rheumatologist for a suspected rare disease. Overgoing numerous tests the final diagnosis was that of Alkaptonuria.

The patient's orthopedic surgical history begins with a right knee replacement in 2007 due to arthritic pain, followed by a left knee replacement for the same reason in 2014. In 2019 he is examined in our facility for pain at the hips with consequent difficulty in the deambulation.

At the physical examination we noticed the presence of dark blue pigmentations in the auricles, sclera and nose typical of the formerly diagnosed disease (Figure 1). At the time we also found him with an arthritic picture of multiple articulations that led us to schedule a right hip replacement.

During surgery we encountered the dark blue discoloration in joint surfaces, ligaments, tendons and muscular fibers. At

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a month's distance, the patient benefited of some pain relief and showed improvement in walking and articulatory range of motion.

Case Report #2

The second patient of age 67, female, comes to our attention with severe joint limitation of the left knee, deficit of active extension of the leg on the thigh and intense pain in the load and active and passive mobilization. The patient had previously undergone right knee replacement surgery and aortic valve replacement surgery. At the time of the visit, the patient already had a diagnosis of alkaptonuria. Given the clinical picture of the patient with severe three-compartment osteoarthritis, we decided for a left knee replacement surgery. The patient had a longer than normal post-operative course, with the presence of complications such as anemia and deep vein thrombosis of the tibial veins linked to prolonged lodging. After the operation, however, the patient recovered a good range of mobility and presented a reduction in pain (Figures 2 and 3).

Discussion

Alkaptonuria is a rare autosomal recessive metabolic genetic disease in which there is a reduction in homogentisic acid oxidase enzyme. The first sign of alkaptonuria is often a change in the color of the urine. Initially there is the involvement of the intervertebral joints,[23-24] with sclerosis of the discs and osteoporosis of the vertebral bodies. Alkaptonuric ochronosis is an uncommon cause of arthropathy, being a rare disease, in fact it can be diagnosed intraoperatively when the presence of bluish-black discoloration of some connective tissues is found or post-operatively.[25-26]

Alkaptonuria is a disease that currently does not provide a cure, except liver transplantation (an organ that produces homogentisin oxidase), but only symptomatic treatment that consists of non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular steroid injection, and ascorbic acid.[17] For problems related to large joints, initially the treatment is conservative, but subsequently there is the possibility of totally hip and knee replacements with apparently good results in terms of symptoms and functionality, although almost none of the reviews available in the literature include a sufficient number of patients affected by ochronosis by evaluating their specific functional outcames or specific procedural difficulties related to surgery and implants selection.[27-30]

Conclusions

Alkaptonuria is a rare metabolic disease that involves the involvement of the spine and large joints. At the moment

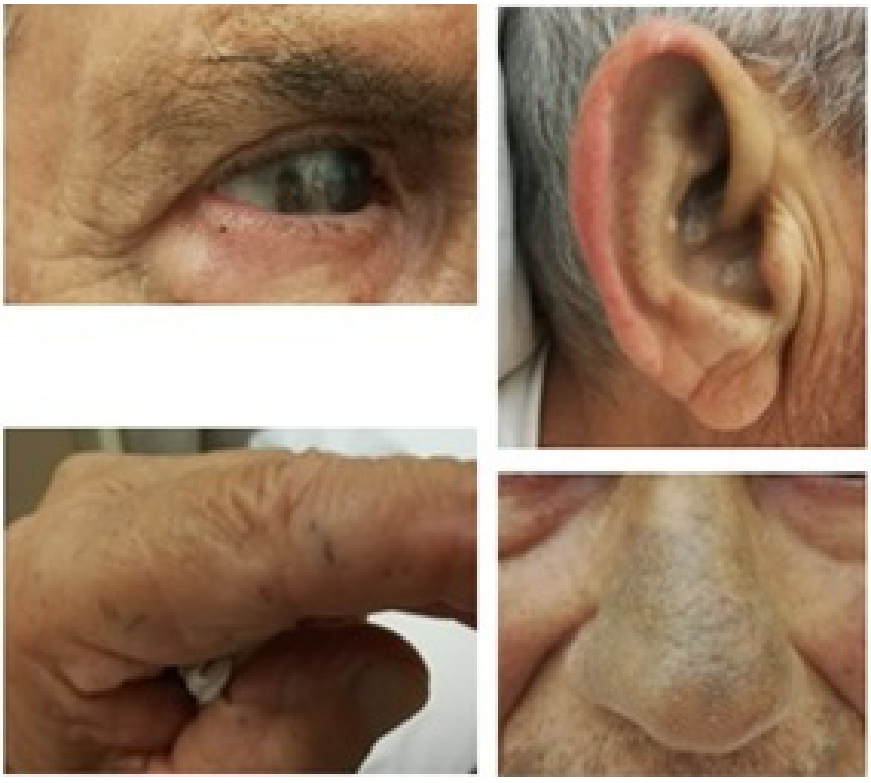

Figure 1. Dark blue pigmentations in the auricles, sclera and nose.

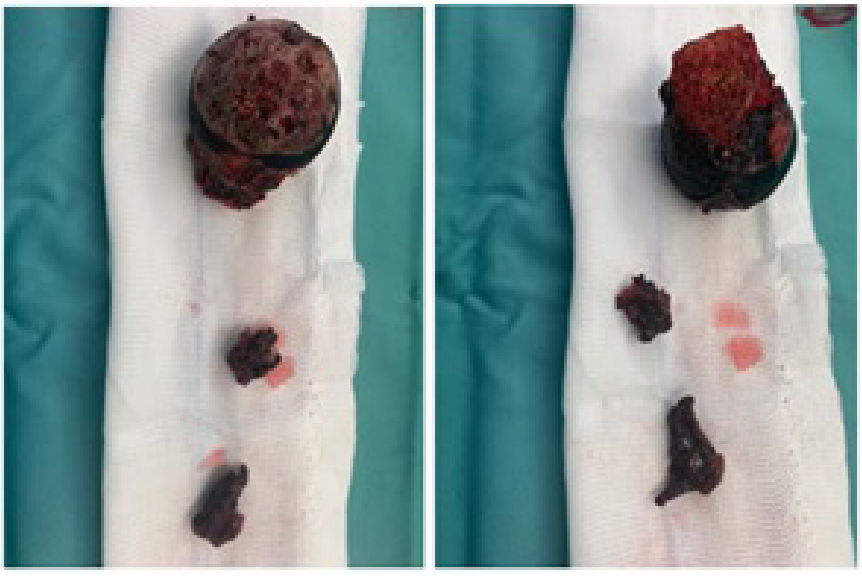

Figure 2. Ochronotic joint manifestation: intraoperatively resected head of femur and soft tissue removal.

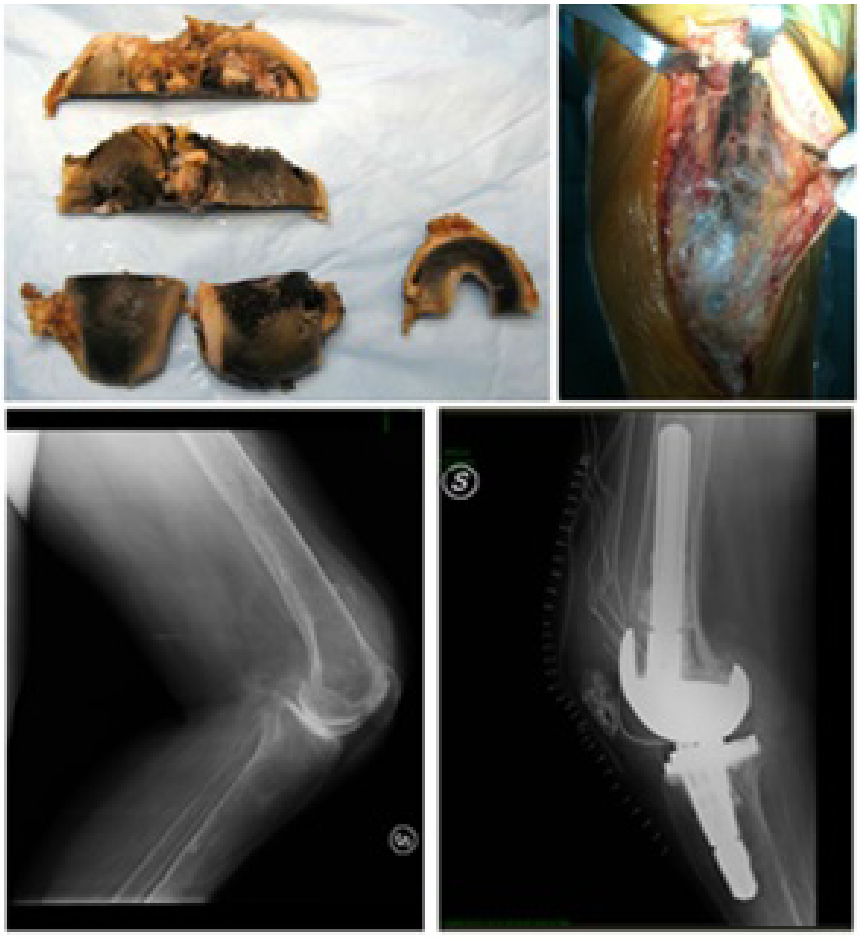

Figure 3. Intraoperatively knee joint surfaces, lateral radiograph of total knee prosthesis.

there are no treatments that allow the resolution of the disease. From an orthopedic point of view, you can act by replacing the joints involved, giving a benefit both in movement and in reducing pain.

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