



Case report

Long-term follow-up of bilateral hip and knee arthroplasty secondary to ochronotic arthropathy

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ABSTRACT

Alkaptonuria is a rare metabolic disorder caused by the deficiency of homogentisic acid oxidase enzyme, which is responsible for eliminating homogentisic acid from the body through the renal system. Excessive accumulation of homogentisic acid leads to ochronosis and ochronotic arthritis. Owing to the rarity of the disease, long-term functional outcomes of joint replacements of the hips and knees in ochronosis arthropathy are unconfirmed, and only a limited number of case reports are available on this. We present a case of a 45-year-old man with ochronosis and advanced osteoarthritis of both the hips and knees. He underwent bilateral hip and knee replacements as staged procedures. At a follow-up of more than 12 years, the man had full mobility with no loosening of implants.

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Introduction

Alkaptonuria is a rare disease of amino acid metabolism affecting 1 in 1 million people [1]. It is caused by autosomal recessive mutations of the homogentisic acid (HGA) oxidase (HGO) gene on chromosome 3q [1]. In affected individuals, a defect in HGO, which cleaves HGA into maleylacetoacetic acid, causes an excessive pooling of HGA resulting in ochronosis, destruction of the connective tissue and excretion of large quantities of HGA in urine [1].

Ochronosis is deposition of grossly bluish black but microscopically ochre (meaning yellow in Greek) pigmented remnants of the metabolite in connective tissues, especially hyaline articular cartilage. The deposition eventually leads to degenerative arthropathy of large joints such as the hip and knee joints and may cause disability and affect quality of life for affected individuals at a young age. Typically, the pigmentation is seen in the affected joints perioperatively [2]. This type of arthropathy usually manifests in the fourth decade of life [3]. The usual clinical findings associated with alkaptonuria include pigmentation of the skin, sclera, and ear cartilage

and discoloration of urine. Ochronotic arthropathy usually involves the spine first and large joints subsequently [4]. Less common manifestations include renal, urethral, and prostate calculi and deposition in cardiovascular system, especially the valves. To date, there is no known curative treatment for alkaptonuria [5].

Systemic metabolic diseases cause diminution in bone density, and only limited cases of ochronotic arthropathy can be found in the medical literature because of the rarity of the disease [6–9]. This report presents the case of a man with bilateral hip and knee ochronotic arthropathy who underwent arthroplasty for all affected joints with a long-term follow-up of 12 years.

Case history

A 45-year-old man was admitted to the Orthopedic Surgery Department of our hospital in 2002 with severe limitation of movement and pain in both the hips and knees over a period of 3 years. He was wheelchair-bound and he was on regular analgesic medication. Previous nonoperative treatment had failed to improve his condition. Physical examination revealed joint extension of 0°, flexion of 60°, internal rotation of 0°, and external rotation of 30° in both the hips. Faber test was positive. Exam also revealed a range of motion of 10°–90° in both the knees. Destructive narrowing at the joint space, acetabular protrusion, subchondral cysts, and sclerosis were observed on plain radiographs (Fig. 1). Degenerative

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osteophytic changes and osteophyte formations with narrowing and sclerosis of the medial joint space in all compartments of both the knees were also observed on plain radiography. Because of the advanced stage of osteoarthritis in both the hips and knees, staged total hip and knee replacements were recommended. The man had no medical history of systemic involvement, dermatological or ocular changes or episodes of dark urine, so there was no clinical indication of systemic disease.

First, a right total hip arthroplasty was planned. During the surgery, after a wide capsular resection, the femoral head was dislocated and markedly brown-black discoloration of the joint capsule, femoral head and acetabular cartilage was observed (Fig. 2). A strong synovial reaction was noted, and multiple tissue samples were obtained for culture and fresh frozen histopathological analysis. A cementless total hip arthroplasty was performed without any intraoperative challenges. Histopathology showed extensive histiocytic cells around the pigmented, degenerated cartilage and deposition of particles on the surface of the joint scattered on the cartilage with the development of irregular fibrotic tissue. The man was diagnosed as having ochronosis on the basis of the intraoperative findings and radiographic and histopathological examinations.

Three months later, a left cementless total hip arthroplasty was performed, with features similar to that of the right hip, with extensive blackening of the femoral head and soft tissues. Analysis of the collected samples was similar to the findings on the right hip. He received a standard rehabilitation program. Harris hip score [10, 34] improved from poor (below 60, preoperatively) to excellent (87, last follow-up in September 2019). Radiographs showed stable prostheses with no evidence of subsidence (Fig. 1). The man

experienced complete pain relief and there were no complications or revision surgery.

The man did not experience any episodes of alkaptonuria or dark urine during the period of the follow-up. He had advanced ochronotic arthropathy in hip knee joints, which hindered his daily routine and rehabilitation. Owing to his aggravated knee problems, he was admitted again for staged total knee replacements 6 months after the left hip replacement. Total knee arthroplasty of the right knee was performed with a midline incision and medial parapatellar arthrotomy. During the surgery, brown-black discoloration of the tibial condyles, femoral condyles, meniscus, and joint capsules was observed. However, as the diagnosis was known, histopathology samples were not collected. Although the joint surface of the patella was not eroded enough requiring patellar component application, it was replaced because of the brown-black discoloration of the cartilage (Fig. 2).

Total knee arthroplasty of the left knee was performed 6 weeks after the right knee arthroplasty, and the findings were similar to those of the right knee. No complications occurred during the surgery, and the man was able to move on the second postoperative day with complete pain relief. The postoperative period after both the surgeries was uneventful, and the man was compliant with rehabilitation. After 3 months of extensive rehabilitation, he demonstrated total independence in activities of daily living with an excellent range of motion (0–110°) (Fig. 3). He did not require further pain medications. Knee Society knee scores [11] improved from poor (below 60, preoperatively) to 93 on the last follow-up (in September 2019). He started driving and never complained of any residual symptoms. We followed him up for more than 12 years with no major complications. At the most recent follow-up in September 2019, all prostheses were found to be working well with



Figure 1. Preoperative radiograph images of the hips showing gross loss of joint space suggesting features of osteoarthritis, whereas the last postoperative radiograph images (September 2019) showing the implantation of bilateral hip prosthesis.



Figure 2. Intraoperative images of the hip (left) and one of the knees (right) showing severe ochronotic involvement with blackish discoloration of the joint.

no signs of loosening (Figs. 1 and 2). The man is satisfied with the treatment outcomes, and he is being followed up in the clinic annually. He provided a consent for publishing his case along with its related clinical information and images.

Discussion

Sir Archibald Garrod described alkaptonuria as the first disorder in humans that obeys the principles of Mendelian autosomal



Figure 3. Preoperative radiograph images of the knees suggesting features of severe osteoarthritis, whereas the last postoperative radiograph images (September 2019) showing implantation of bilateral knee prosthesis.

Table 1
Brief description of case reports published regarding ochronotic arthropathy.

Author	Year	No. of patient	Joint	No. of joint replaced	Age	Gender	Follow-up	Preoperative measurement	Postoperative measurement
The present study	2020	1	Bilateral knee and bilateral hip	4	45	Male	12 y	Knees ROM: 10–90, KSS: Poor (less than 60) Hips ROM: 0–60, HHS: Poor (less than 60)	Knees ROM: 0–110, KSS: 92 Hips ROM: 0–115, HHS: 87
Lee et al. [17]	2019	1	Bilateral knee	2	54	Male	2 y	Right ROM 5–100, left ROM 15–90.	OKS: 40, KSFS: 70, KSKS: 73 bilateral.
Di Marco et al. [18]	2019	1	Bilateral knee and bilateral hip	4	50	Female	7 y	OKS: 9. KSFS: 0 Right knee ROM: 5–100, left knee ROM: 0–120, right hip ROM: 0–85, left hip ROM: 0–90	ROM: 0–90 bilateral Right knee ROM: 0–110, left knee ROM: 0–120, right hip ROM: 0–95, left hip ROM: 0–100
Fernando et al. [19]	2018	1	Bilateral hip	2	69	Female	18 mo	None	Independently ambulant and pain free with no complaints. Radiograph looks fine
Mazoochy et al. [20]	2018	1	Right knee and right hip	2	57	Female	2 y	Unknown	Results are satisfactory
Karaoğlu et al. [6]	2016	1	Left knee	1	55	Male	10 y	ROM: 0–120. No laxity	None. Full activity, no pain, satisfied with outcome. Radiograph looks fine
Patel [9]	2015	1	Right knee	1	58	Female	18 mo	Antalgic gait. ROM: 0–95	KS: 84. Radiograph looks fine
da Silva Martins Ferreira et al. [21]	2014	1	Bilateral knee	2	67	Male	Right: 18 mo. Left: 6 mo	Unknown	Right knee ROM: 0–110. Left knee ROM: 0–120. Asymptomatic, walks without gait support
Sahoo et al. [22]	2014	1	Bilateral knee	2	51	Male	28 mo	ROM 10–20 bilaterally	Walking pain free. ROM 0–90 bilaterally. Radiograph looks fine
Harun et al. [23]	2014	1	Left knee and right hip	2	60	Female	Unknown	Independent ambulation. Antalgic gait. Left knee ROM: 10–110	None. Adequate ROM, free of pain. Radiograph looks fine
Cebesoy et al. [24]	2014	1	Right hip	1	64	Male	6 mo	2-cm shortening of the right lower extremity. The abduction and the adduction were limited by 10 degrees compared with the other hip. Flexion contracture of 15 degrees.	Pain free, had a fully mobile hip joint, and was extremely satisfied with the result
Acar et al. [25]	2013	1	Right hip and left knee	2	62	Female	18 mo	Unknown	None. Adequate ROM and pain free. Radiograph looks fine
Ozmanevra et al. [26]	2013	1	Bilateral knee	2	69	Male	2 y	BMI 30.2. Right ROM: 0–110. Left ROM: 0–114	Bilateral ROM 0–114. HHS score 95 bilaterally. Radiograph looks fine
Gowda et al. [27]	2013	1	Left hip	1	60	Female	2 y	Painful gross restriction of left hip movements with 5 cm shortening.	Pain free, no evidence of loosening of the implant, satisfied with the outcome.
Reed et al. [28]	2012	1	Left knee	1	55	Female	3 mo	Independent ambulation. Antalgic gait. ROM 5–120. No laxity	Excellent stability, pain relief, ROM 0–110. Radiograph looks fine

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Table 1 (continued)

Author	Year	No. of patient	Joint	No. of joint replaced	Age	Gender	Follow-up	Preoperative measurement	Postoperative measurement
Abimbola et al. [29]	2011	1	Left knee	1	48	Male	2 y	Independent ambulation. ROM: 0–130. No laxity	None. Full activities, no pain, very satisfied
Araki et al. [30]	2009	1	Bilateral knee	2	56	Male	6 y	None	Pain free, returned to relatively normal activities. Walking well with crutches
Kopeć et al. [31]	2007	1	Bilateral knee	2	66	Female	Unknown	Right ROM 0–90, left ROM 0–100	ROM 0–100 bilaterally. No pain
Fisher and Davis [16]	2004	1	Bilateral knee and right hip	3	64	Female	3 y	None	None. Able to walk without walking aids
Spencer et al. [32]	2004	1	Unknown knee	1	62	Female	7 y	Unknown	None. Asymptomatic. Independently mobile. Radiograph looks fine
Demir [33]	2003	1	Bilateral knee	2	70	Male	14 mo	Unknown	None
Moslovac et al. [34]	2003	1	Bilateral knee and right hip	3	62	Male	7 y	None	Right hip ROM: flexion: 90°, abduction: 40°. Able to walk with crutches without limitation.
Aydoğdu et al. [35]	2000	1	Left knee	1	48	Male	4 y	Walks with cane, 10 minutes, ROM: 25–125. KSKS: 35, KSFS: 45	ROM 5–120. KSKS: 85. KSFS: 50 (limited by hip, contralateral knee, and spine). Radiograph looks fine
Ayanci et al.	2000	1	Bilateral hip	2	53	Female	3 mo	None	Radiograph looks fine

ROM, range of motion; OKS, Oxford Knee Score; KS, Knee Society clinical rating system; KSKS, Knee Society knee score; KSFS, Knee Society function score; HHS, Harris hip score; KSS, Knee Society Score.

recessive inheritance [1]. In this disease, due to the absence of HGO, HGA cannot be converted to maleylacetoacetic acid, resulting in accumulation of HGA and its oxidation product benzoquinone, which triggers tissue injury [12]. Accumulation of HGA causes the classic clinical triad: homogentisic aciduria, gradual development of ochronosis, and degenerative ochronotic arthropathies. Cardiac involvement in alkaptonuria is rare and mainly manifested as valvular calcification [13]. As renal clearance of HGA decreases with age, clinical manifestations of alkaptonuric ochronosis are usually delayed, not appearing until the fourth decade of life [14]. This could be explained by the remarkable allelic heterogeneity that characterizes alkaptonuria. People with alkaptonuria are either homozygous or compound heterozygous for the loss of function mutation(s) in HGO. This could explain why our patient did not manifest any other signs and symptoms of alkaptonuria, except ochronotic arthropathy in the fourth decade of his life and why the diagnosis of alkaptonuria was made intraoperatively [15].

Ochronotic arthropathy is a sequela of alkaptonuria, affecting large weight-bearing joints [3]. Currently, no definitive medical treatment is available for alkaptonuric ochronosis; the condition is generally managed conservatively. To reduce urinary HGA excretion, dietary restriction of ascorbic acid and amino acids such as phenylalanine and tyrosine is suggested, which may reverse bone abnormalities [16]; however, no reliable information is available to confirm these findings. Nitisinone is a triketone herbicide and potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase which could possibly reduce urinary HGA excretion up to 70% [16]. Long-term effectiveness of nitisinone therapy in treating ochronosis is being evaluated. Joint replacement is offered for patients with

severe degenerative arthropathy. As alkaptonuria is a metabolic disorder of the bones and joints, it affects the mechanical properties of connective tissue, especially the cartilage, and decreases bone quality. To date, only a few case reports with short-term follow-up have described arthroplasty in ochronosis (Table 1). Our study describes the promising outcomes of arthroplasty in an alkaptonuric patient with ochronotic arthritis.

Summary

The male patient in our study underwent bilateral hip and knee replacements with more than 12 years of follow-up, and no complications were encountered. His condition improved significantly, and he returned to activities of daily life without experiencing any pain. The functional outcomes of the surgery, as evaluated by Harris hip score and Knee Society knee scores, were satisfactory. The present study demonstrates that arthroplasty can have excellent outcomes and great prosthesis survival in alkaptonuric patients with ochronotic arthritis, supporting the findings of previously published case reports.

Conflict of interest

The authors declare there are no conflicts of interest.

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