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Mini Review

The Black Bone Disease: Is There A Gender Difference In Prevalence Of Ochronotic Arthropathy? An Epidemiological Overview.

Lorenzo Monti[1], Annalisa Santucci[2], Vincenzo Salini[1], Filippo Maria Anghilieri[3], Andrea Bobba[4], Daniela Braconi[2], Emanuele Franchi[5], Carlo Eugenio Zaolino[6] and Francesco Verde[1].

1. *IRCCS Ospedale San Raffaele, Milan. Italy*
2. *Department of Biotechnology Chemistry and Pharmacy, University of Siena, Siena, Italy*
3. *S. Leopoldo Mandic Hospital, Merate, Italy*
4. *University of Milan, Milan, Italy*
5. *Villa Aprica Clinical Institute Como Italy*
6. *Istituto Ortopedico Gaetano Pini-CTO, Milan, Italy.*

Abstract

Alkaptonuria (AKU) is a rare inherited metabolic disease associated with various clinical and radiological abnormalities due to homogentisic acid deposition. Ochronotic arthropathy is the musculoskeletal manifestation that occurs in patients with AKU, and it is often an occasional finding during joint replacement surgery. Since AKU is known to have an autosomal recessive transmission, its prevalence should not show any gender discrepancy. Despite this, the authors' clinical experience suggested a marked prevalence in the male sex, with patients undergoing hip and knee joint replacements: we investigated the current literature to observe whether our case series was an exception. A systematic review was performed on PubMed, Scopus, and Embase with different combinations of the keywords "ochronosis", "alkaptonuria", "prosthesis", "total joint replacement". Search yielded 157 studies, on which we performed a primary evaluation. As there are no specific orthopaedic registries for this condition, we collected the sex prevalence of ochronosis from case reports and case series in the literature. Overall, from the studies suitable for inquiry, we collected a total of 195 patients with ochronotic arthropathy who underwent joint replacement surgery. Of these, 124 were males and 67 females. We speculate that due to environmental factors, such as work or sports activity, chondral cloth damage causes elevated formation of chondral debris, triggering the apoptotic process, known to be ochronotic arthropathy damaging process: Environmental factors should, in our opinion, explain the gender difference observed.

Keywords : ochronosis; alkaptonuria; THR; TKR; prosthesis.

INTRODUCTION

Alkaptonuria (AKU) was the first genetic disease ever identified as such, by Archibald Garrod, MD in 1901 in London [1]

AKU is a rare metabolic disease transmitted on an autosomal recessive way that affects 1 to 9 people out of 1 000 000 all over the world, caused by a mutation of the homogentisate 1,2-dioxygenase (HGD) gene. The HGD gene contains instructions for creating (encoding) an enzyme known as homogentisate 1,2-dioxygenase. This enzyme is essential for the breakdown of homogentisic acid. Mutations of the HGD gene result in deficient levels of functional homogentisate 1,2-dioxygenase, which, in turn, leads to excess levels of homogentisic acid (HGA) [2].

It is reported to be more prevalent in some countries like Dominican Republic and Jordan with the highest prevalence in Slovakia (1 in 19,000) [2-3].

Alkaptonuria is inherited as an autosomal recessive trait. Recessive genetic disorders occur when an individual inherits the same abnormal gene for the same trait from each parent. Thereby, being an autosomal recessive disease, AKU is not expected to have any sex prevalence. Conversely in the clinical practice of the authors, Orthopaedic surgeons with expertise in hip and knee replacement surgery, most patients are male [4].

The present systematic review aims to assess the prevalence

***Corresponding Author:** Dr. Filippo Maria Anghilieri, S. Leopoldo Mandic Hospital, Merate, Italy. **E-mail:** filippo.anghilieri@gmail.com
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of ochronotic arthropaty in male and female sexes based on current literature evidence.

Pathogenesis

The disease is characterized by the accumulation of homogentisic acid (HGA) and benzoquinone acetic acid (BQA), a product of its oxidation, in different tissues (cartilage, connective tissues) and body fluids (urine, sweat) resulting in clinical manifestations such as dark urine, blue-gray coloring of the eye sclera and helix of the ear (ochronosis), and a disabling arthropathy especially in the large axial and peripheral joints (ochronotic arthropathy) [5].

Tissue damage is secondary to the deposition of a melanin-like pigment that shows high affinity for connective tissue. This pigment triggers several oxidoreduction reactions and induces the production of free radicals, further damaging connective tissue [5].

Despite the disease is present since birth, clinical manifestations become clear after the third decade, when patients begin to develop abnormal pigmentation of the sclera and skin covering the cartilage, associated with back-pain and stiffness. Large joint involvement is usually delayed, and results in end-stage joint disease.

Instead, the presence of dark spots in the diaper may help in early diagnosis.

Patients may present with ankylosis and fractures of the vertebrae and long bones. Additional clinical manifestations are genito-urinary (renal, bladder, and prostatic stones) and cardiac (mitral valvulopathy, arrhythmias) complications, and respiratory failure caused by musculoskeletal involvement.

Diagnosis

Definitive diagnosis is posed on genetic testing, but the disease can be suspected in cases that are not clinically evident. One pathway may be to assay HGA levels in urine by gas chromatography-mass spectroscopy. Since not many patients present with dark urine, it may be useful to analyze HGA levels in all patients who present with evidence of arthropathy on radiography.

Radiographs of the spine show disc degeneration associated with dense calcification, particularly in the lumbar region.

Differential diagnosis should be considered with acute intermittent porphyria, rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.

Clinical management

Currently, treatment is only palliative. A targeted diet with low protein intake may be beneficial, but compliance is often limited.

Use of painkillers combined with physiotherapy helps reduce pain and improves joint range of motion.

Arthrodesis of vertebral discs (lumbar in particular) and/or joint replacement of the knee, hip, or shoulder is often required.

Over the years, therapeutic strategies have been investigated to modify the altered phenylalanine-tyrosine metabolic pathway, for example, with Nitisone (NTBC), which with the multicenter randomized clinical trial called SONIA 2 showed a reduction in the rate of disease progression in subjects receiving NTBC compared to controls [2].

The mechanism of NTBC exploits the inhibition of the enzyme 4-hydroxyphenyl pyruvic oxidase to prevent the formation of downstream metabolites (HGA).

Still the minimum necessary dose and the most appropriate time to start therapy need to be evaluated, but the results are promising.

Prognosis

Life expectancy is not significantly reduced, but the disease mostly impairs the quality of life (QOL), often leading the patient to very disabling functional decline, forcing him or her to use crutches or a wheelchair.

Cardiac complications can worsen the prognosis.

Orthopaedic implication

From the orthopedic perspective, the most important manifestations are ochronotic spondylitis and ochronotic arthropathy, which mainly affects large joints (knee, hip, and shoulder).

The mechanism underlying this early degeneration appears to be at the charge of HGA, which as shown in the study by Galderisi et al [3] if present at elevated levels at the chondral level results in blockage of normal autophagy flux (elimination of cellular debris) and activation of the apoptotic pathway (cell death) mediated by oxidative stress, mitochondrial damage, alteration of nucleolar morphology and deposition of ochronotic pigment.

Typically, the earliest symptoms appear in the fourth decade of life, with evidence of increasingly bulky (and irregular) calcifications and narrowing of the space between the vertebral discs.

The management of either of these clinical manifestations is comparable to that of a classic osteoarthrosic-degenerative disease in a patient without Alkaptonuria.

In our clinical practice, although it is a rare condition, it has occasionally occurred to make an intraoperative diagnosis of ochronosis.

Once an intraoperative diagnosis was placed, the patients were referred to centers specialized in the diagnosis and treatment of rare diseases so that they could be included in appropriate treatment protocols.

In the last 3 years four patients received a diagnosis from our group in the OR. They were all male, with an age ranging from 54 and 65 years.

In addition, 4 Patients (3 males and 1 female) with definite diagnosis and undergoing drug treatment underwent knee or hip replacement

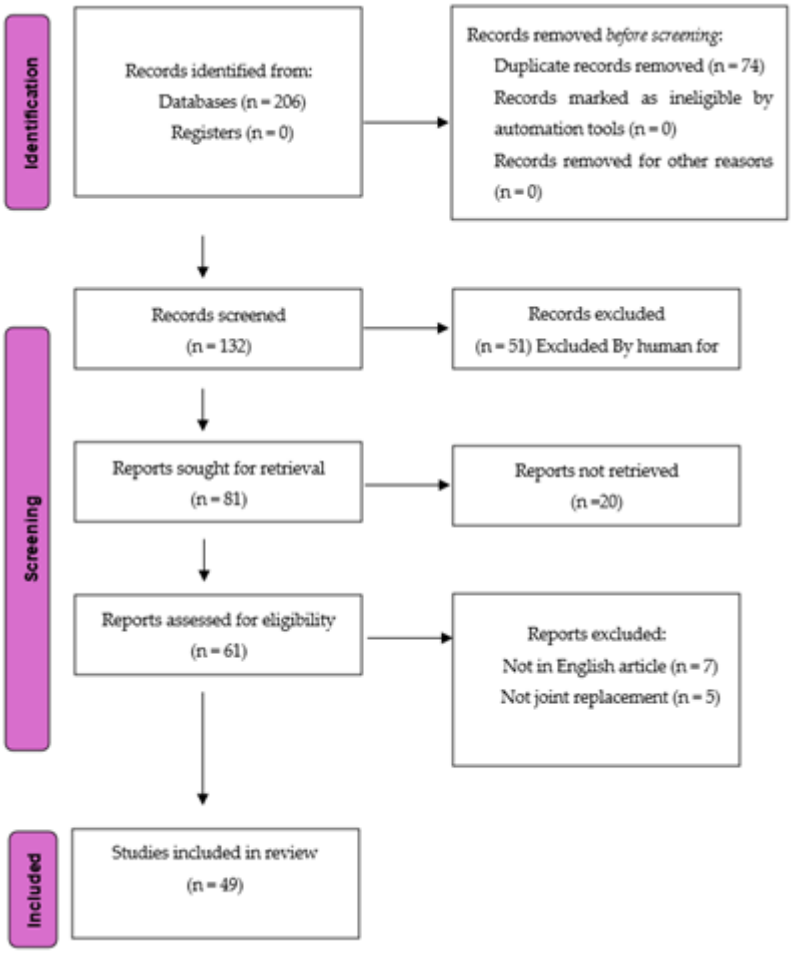
Given that this is a genetic disorder with autosomal recessive transmission, we investigated, intrigued by the high incidence of large joint osteoarthritis in the male sex, the current literature to observe whether our case series was an exception.

MATERIALS AND METHODS

We conducted a comprehensive literature search using PubMed/Medline (National Library of Medicine, Washington, DC) and Embase (Excerpta Medica dataBASE by Elsevier) from 1st January 1965 to 31st December 2023, since to the best of our knowledge the first reports of chondrosis dissecans ochronotica of joints dates to the early 1960s. The following string was used to perform the literature search: “ochronosis arthroplasty”.

The titles and abstracts of the identified articles were screened by two independent reviewers (AB and LM) and checked for agreement. Disagreement was solved through debate, involving the other authors. The studies included during the screening phase were read in full and evaluated based on the stated eligibility criteria. Reference lists of potentially relevant original articles were hand-searched to identify any remaining study, unidentified in the previous steps. Once again, the articles were checked for agreement among the authors (**Figure 1**).

Figure 1. PRISMA flowchart.



All the following criteria had to be satisfied to determine study eligibility: (i) original clinical studies, case series, case reports (ii) written in English, (iii) Gender specification of the patients included, (iv) articles reporting patients undergoing total joint replacement,

RESULTS

The initial search yielded 206 studies that were screened for eligibility and 157 studies, which did not fulfil the eligibility criteria, were excluded. In total, 49 studies were included and processed for final data extraction.

From the articles included in the present review, we collected a total of 170 patients with ochronotic arthropathy who underwent joint replacement surgery.

Of these 108 were males (63.5%) and 62 were females (36.5%). From the 170 patients included, considering only joint replacements of the three major joints (hip, knee and shoulder), we collected a total of 216 implants. This of course means that some patients underwent replacement of more than one joint. We gathered 90 hip replacements, 91 knee replacements, and 35 shoulder replacements. (**Table 1**).

Table 1.

Author	n	M	F	hip	knee	shoulder
Zmerly ed al - 2019	1	1	0	1	1	0
Arasu et al - 2022	3	2	1	3	0	0
Arora et al - 2023	2	1	1	0	2	0
Patel et al - 2015	1	0	1	0	1	0
Kumps et al - 2021	1	1	0	1	1	0
Al Dosari - 2020	1	1	0	0	1	0
Di Matteo et al - 2021	1	1	0	0	1	0
Ranganath et al - 2021	87	55	32	36	46	31
Wu Chean Lee et al - 2019	1	1	0	0	1	0
Pesciallo et al - 2022	2	2	0	0	2	0
Kozanhan et al - 2018	2	1	1	0	1	0
Jiang et al - 2019	1	1	0	0	1	0
Sabater et al - 2020	1	0	1	0	1	0
Holzer et al - 2013	1	0	1	1	0	0
Merolla et al - 2012	1	1	0	0	0	1
Kefeli et al - 2008	2	0	1	1	1	0
Visser et al- 2021	1	1	0	0	1	0
Mohapatra et al- 2014	1	1	0	1	0	0
Jasper et al - 2016	1	1	0	0	0	0
Moslavac et al - 2003	1	1	0	1	1	0
Pachore et al - 2019	10	6	4	10	0	0
Cebesoy et al - 2014	1	1	0	1	0	0
Rajkumar et al -2020	16	12	4	15	12	0
Da Silva Martins Ferreira et al - 2014	1	1	0	0	1	0
Dawod et al - 2023	1	1	0	0	0	1
Jirel et al - 2022	1	1	0	1	0	0
Karaoglu et al - 2016	1	1	0	0	1	0
Aynaci et al - 2000	1	0	1	1	0	0
Yap San Min et al- 2023	1	1	0	1	0	0
Kitahara et al - 2021	1	1	0	1	0	0
Ogata et al - 2008	1	0	1	1	0	0
Al-Ajlouni et al - 2020	5	2	3	4	4	0
Demir - 2003	1	1	0	1	1	0
Saini et al- 2021	1	1	1	0	0	0
Mohan Sahoo et al - 2014	1	1	0	0	1	0
Syam et al - 2021	1	1	0	0	1	0
Reed et al - 2012	1	0	1	0	1	0

Drakoulakis et al - 2012	1	1	0	0	0	2
Aydogdu et al - 2000	1	1	0	0	1	0
Fernando et al - 2018	1	0	1	1	0	0
Mazoochy et al - 2018	1	0	1	1	1	0
Shaihk et al- 2020	1	0	1	0	1	0
Harun et al - 2014	1	0	1	1	1	0
Abimbola et al - 2011	1	1	0	0	1	0
Ali Acar et al - 2013	1	0	1	1	1	0
Araki et al - 2009	1	1	0	1	1	0
Gowda et al - 2013	1	0	1	1	0	0
Shimizu et al - 2007	1	0	1	1	0	0
Cetinus et al - 2005	2	1	1	2	0	0
TOTAL	170	108	62	90	91	35

DISCUSSION

Ochronotic arthropathy is a joint manifestation that occurs in patients with alkaptonuria. Although this metabolic disorder is not known to have a gender discrepancy, both in the authors' clinical practice and in the findings of the present review, a preponderance of male patients appears.

From a purely genetic point of view, it is not possible to justify this finding.

Indeed, the articular damaging mechanism of the pathology is known to be a degeneration of chondral and subchondral tissue caused by the deposition and accumulation of HGA. This results in a blockage of regular autophagic flux (elimination of cellular debris) and activation of the apoptotic pathway (cell death) mediated by oxidative stress, mitochondrial damage, alteration of nucleolar morphology, and deposition of ochronotic pigment.

Noting this, we speculate that this tissue impairment is more represented in the male sex, where due to environmental factors, such as work or sports activity, chondral cloth damage causes elevated formation of chondral debris, triggering the apoptotic process.

Wear and tear jobs, sports and work-related trauma sequelae are factors favoring the onset of osteoarthritis in the general population. It is assumed that the same environmental factors also cause degeneration and wear and tear to the large joints of patients who are unaware carriers of alkaptonuria.

Chondral and joint damage in these patients, however, will not be managed by the host immune system as in the healthy population: in fact, we know how HGA deposits induce apoptosis and subsequent chronic inflammatory state of chondral and subchondral tissue, leading to massive and permanent damage well provable by diagnostic investigations.

CONCLUSIONS

To the best of our knowledge, through our clinical practice and through the review of modern literature, ochronotic arthropathy is more represented in male sex.

As we have investigated patients who underwent joint replacement surgery, it is appropriate to specify that these results are intended for end-stage arthropathy.

We believe that ochronotic arthropathy is to be regarded as a strongly predisposing substrate for osteoarthritis, on which, however, there is an interplay of environmental factors as well.

These environmental factors account for the gender difference observed.

Since Alkaptonuria is a rare disorder, whose diagnosis is often insidious or misrecognized, it is possible that data in the literature are only the tip of the iceberg.

It is vital therefore to spread the knowledge of this condition also in the orthopaedic world and that patients are sent to referral centers to receive better treatments and to collect further data.

Author Contributions

Material preparation, data collection and analysis were performed by Lorenzo Monti, Filippo Maria Anghilieri, Andrea Bobba and Carlo Zaolino. The first draft of the manuscript was written by Lorenzo Monti and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript. A special thanks to aimAKU Onlus and Sylvia Sestini for helping us on knowing and trying to understand this disease.

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Conflicts of Interest

No funding was received for conducting this study. The authors have no relevant financial or non-financial interests to disclose.

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