CASE REPORT
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Ochronotic knee in a patient with Alkaptonuria

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ABSTRACT

A patient with a not known history of alkaptonuria was admitted for knee osteoarthritis and total joint replacement treatment. During the operation the dark colour of the knee cartilage resembled the clinical manifestation of Ochronosis. Postoperatively the patient was informed and laboratory and imaging studies put the diagnosis of Alkaptonuria. Alkaptonuria is a rare metabolic disorder affecting the connective tissue. Ill patients are usually suffering from joint arthritis and seek for orthopaedic advice and treatment.

KEYWORDS: Alkaptonuria, Ochronosis, Arthritis.

Introduction

Alkaptonuria is a rare inherited genetic disease which is caused by a gene mutation for the enzyme homogentisate 1,2-dioxygenase (HGD). The body accumulates an intermediate substance called homogentisic acid in the blood and tissues. Homogentisic acid and its oxidized form alkapton are also excreted in the urine. All above products give a dark blue-black colour in the tissues especially the connective tissues and the cartilage. This special colour is also known as Ochronosia.

Alkaptonuria was described by Archibald Edward Garrod, as being the result of the accumulation of intermediates due to metabolic deficiencies. He linked ochronosis with the accumulation of alkaptans in 1902, [1-4] In the same period, the genetics of it was also studied by William Bateson .[5] However, the genetic basis was elucidated in 1996, when HGD mutations were demonstrated. [4,6]

A 1977 study showed that an ochronotic Egyptian mummy had probably suffered from alkaptonuria.[7,8] In most ethnic groups, the prevalence of alkaptonuria is between 1:100,000 and 1:250,000. [4] In Slovakia and the Dominican Republic, the disease is much more common, with prevalence estimated at 1:19,000 people. As for Slovakia, this is not the result of a single mutation, but due to a group of 12 mutations in specific "hot spots" of the HGD gene.[4]

Pathophysiology

ll people carry in their DNA two copies (one received from each parent) of the gene HGD, which contains the genetic information to produce the enzyme homogentisate 1,2-dioxygenase (HGD) which can normally be found in numerous tissues

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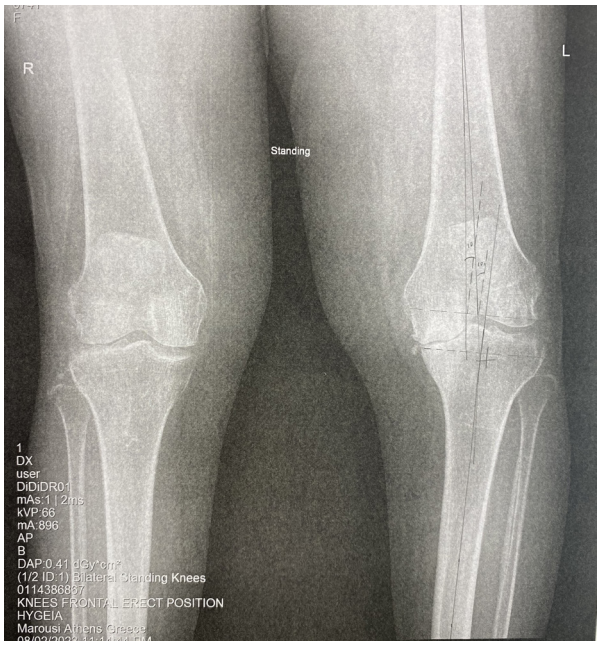

Fig 1. *Pre-operative x-ray showing the severe left knee arthritis and varus deformity*

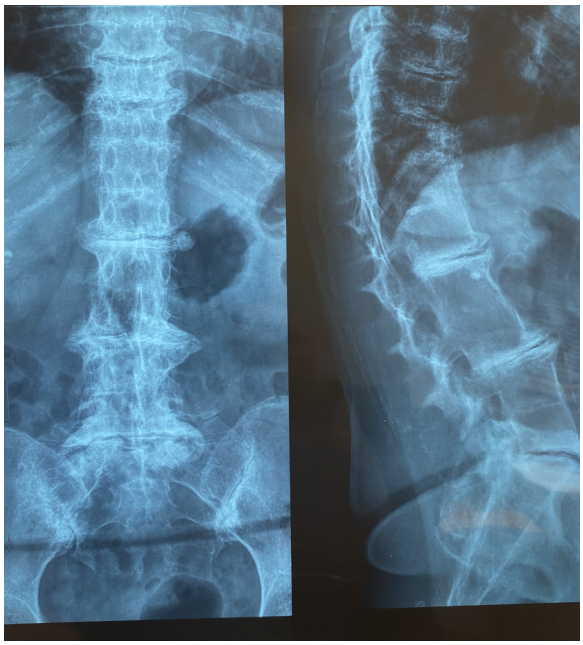

Fig 2. *Lumbar spine x-ray showing the fusion-like vertebral bodies deformity.*

in the body (liver, kidney, small intestine, colon, and prostate). In people with alkaptonuria, both copies of the gene contain abnormalities and the body cannot produce an adequately functioning enzyme. HGD mutations are generally found in certain parts (exons 6, 8, 10, and 13), but a total of over 100 abnormalities has been described throughout the gene. The normal HGD enzyme is an hexamer that is organized in two groups of trimers and contains an iron atom. Different mutations may affect the structure, function, or solubility of the enzyme. Very occasionally, the disease appears to be transmitted in an autosomal-dominant fashion, where a single abnormal copy of HGD from a single parent is associated with alkaptonuria.[1]

The HGD enzyme is involved in the metabolism of the aromatic amino acids phenylalanine and tyrosine. [9] Normally, these enter the bloodstream through protein-containing food and the natural turnover of protein in the body. Tyrosine is specifically required for a number of functions, such as thyroid hormones, melanin and certain proteins, but the vast majority (over 95%) is unused and is metabolized through a group of enzymes that eventually generate acetoacetate and malate. In alkaptonuria, the HGD enzyme cannot metabolize the homogentisic acid (generated from tyrosine) into 4-maleylacetoacetate, and homogentisic acid levels in the blood are 100-fold higher than would normally be expected, despite the fact that a substantial amount is eliminated into the urine by the kidneys. The homogentisic acid is converted to the related substance benzoquinone acetic acid which forms polymers that resemble the skin pigment melanin. These are deposited in the collagen. Therefore, the ochronotic connective tissue is stiffened and unusually brittle, impairing its normal function and causing structural damage.[10]

Clinical manifestations

The paediatrician will be the first physician that will put the diagnosis as dark stains on a baby's diaper are one of the earliest signs of alkaptonuria. The urine may turn dark brown or black when it's exposed to air. [10] By the second and third decades of life the patient may notice signs of early-onset arthritis of the spine or the large joints.

Pigmentation may be noted in the cartilage of the ear and the sclera and corneal limbus of the eye.[10-12] After the age of 30, people begin to

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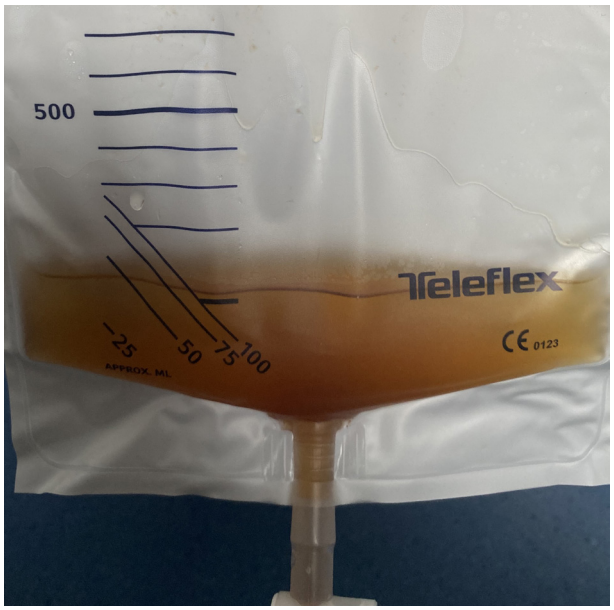

Fig 3. *Orange colour of the urine.*

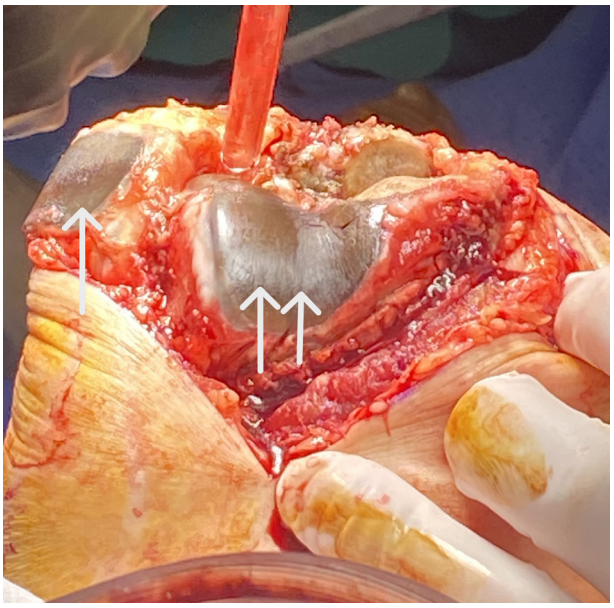

Fig 4. *Ochronosia with an ink- like colour of the patellar cartilage (single arrow) and the trochlea (double arrow).*

Fig 5. *Ochronosia with an ink-like colour of the lateral femoral condyle (single arrow) and severe arthritis without cartilage tissue of the medial femoral condyle (double arrow).*

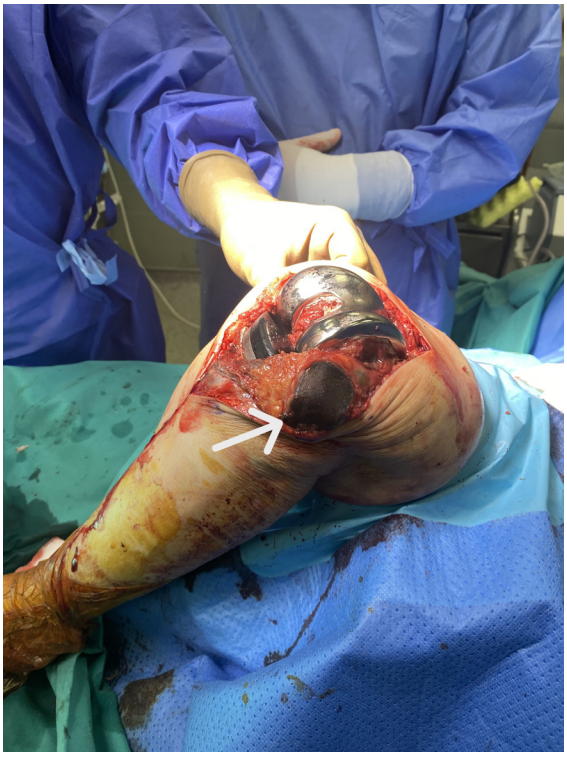

Fig 6. *Despite the ochronotic appearance of the patella cartilage, it was stable and very smooth and the surgeons decided to leave it untreated (arrow).*

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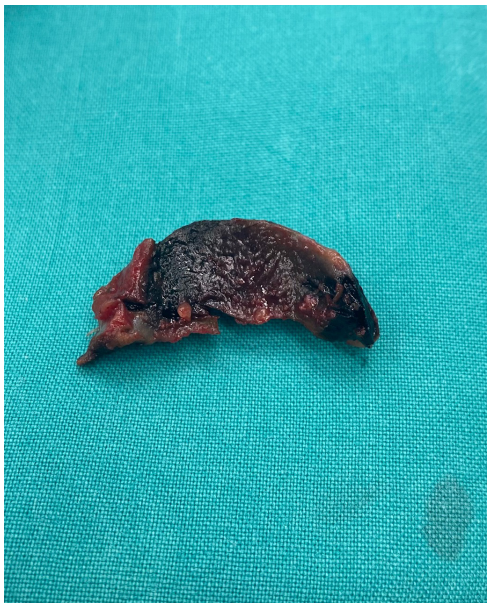

Fig 7. *Black coloured medial meniscus resected.*

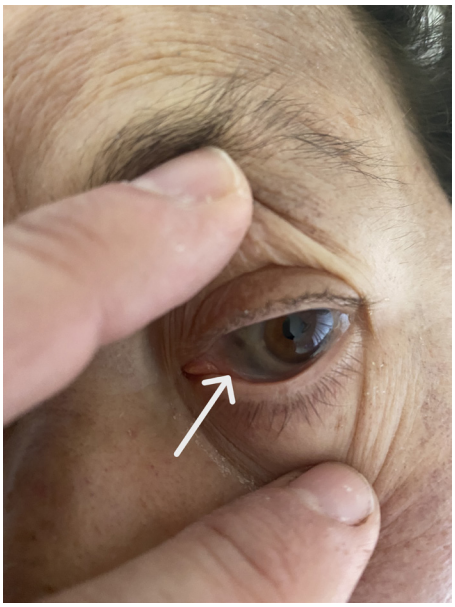

Fig 8. *Black stain of the eye's sclera (arrow).*

develop pain in the weight-bearing joints of the spine, hips, and knees. The pain can be severe to the point that interferes with activities of daily living and may affect the ability to work. Joint-replacement surgery is often necessary at a relatively young age. During such operation, the orthopaedic surgeon is taken by surprise of the dark colour of the cartilage. In the longer term, the involvement of the spinal joints leads to reduced movement of the rib cage and can affect respiratory function. Bone mineral density may be affected, and osteoporosis will increase the risk of bone fractures. Rupture of tendons and muscles may also occur. Valvular heart disease, mainly calcification and regurgitation of the aortic and mitral valves, may occur, and in severe and progressive cases, valve replacement may be necessary. Irregularities in the heart rhythm and heart failure affect a significant proportion of people with alkaptonuria (40% and 10%, respectively). Hearing loss affects 40% of people. Finally, there is a propensity to developing kidney stones exists, gallstones and stones in the prostate and salivary glands (sialolithiasis).[10]

Diagnosis

If the diagnosis of alkaptonuria is suspected, it can be confirmed or excluded by collecting urine for 24 hours and determining the amount of homogentisic acid by means of chromatography. No assay of HGA in blood has been validated. The severity of the symptoms and response to treatment can be quantified through a validated questionnaire titled the AKU Severity Score Index. This assigns scores to the presence of particular symptoms and features, such as the presence of eye and skin pigmentation, joint pain, heart problems, and organ stones.[10]

Treatment

No treatment modality has been unequivocally demonstrated to reduce the complications of alkaptonuria. Main treatment attempts have focused on preventing Ochronosis through the reduction of accumulating homogentisic acid. Such commonly recommended treatments include large doses of ascorbic acid (vitamin C) or dietary restriction of amino acids phenylalanine and tyrosine. However, vitamin C treatment does not have definitively proven effectiveness and protein restriction has not shown to be effective in clinical studies.[10]

Several studies have suggested that the herbicide nitisinone may be effective in the treatment of alkaptonuria. Nitisinone inhibits the enzyme 4-hydroxyphe-

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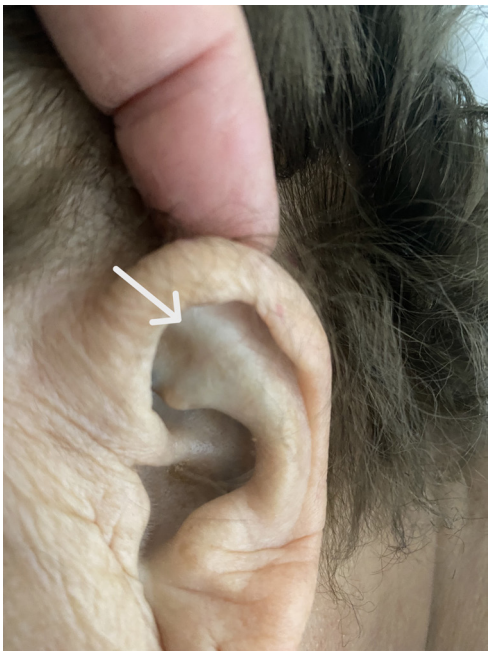

Fig 9. *Blue discoloration of the ear's cartilage (arrow).*

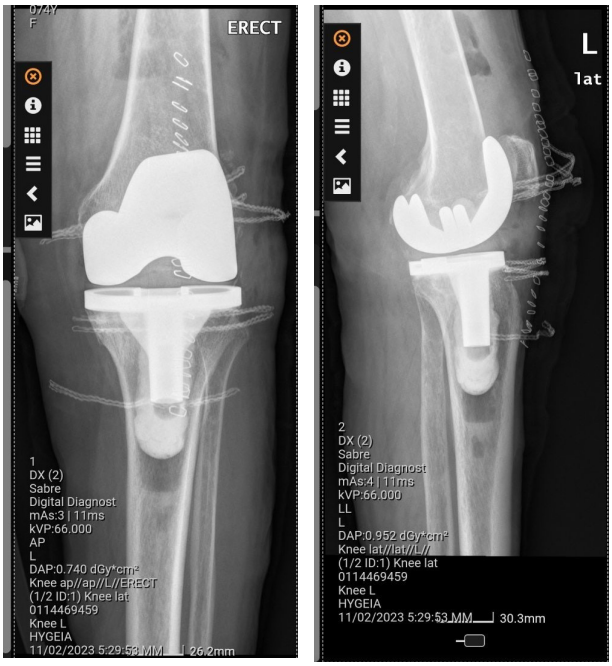

Fig 10. *Postoperative x-rays. (9a and 9b)*

nylpyruvate dioxygenase, responsible for converting tyrosine to homogentisic acid, thereby blocking the production and accumulation of HGA. Nitisinone has been used for some time at much higher doses in the treatment of type I tyrosinemia. Nitisinone treatment has been shown to cause a larger than 95% reduction in plasma and urinary HGA. The main drawback is accumulation of tyrosine, the long-term risks of which are unknown; a particular concern exists about damage to the cornea of the eye. Long-term use requires frequent monitoring for complications.[10] In 2020 the European Medicines Agency approved Orfadin (nitisinone) for the treatment of alkaptonuria in adult patients[13]

In terms of prognosis, alkaptonuria does not appear to affect life expectancy, although the latest study on the topic is from 1985.[10] The main impact is on quality of life; many people with alkaptonuria have disabling symptoms such as pain, poor sleep, and breathing symptoms. These generally start in the fourth decade. The typical age at requiring joint replacement surgery is 50–55 years.

Case report

A 74-year-old lady was admitted for elective total knee replacement due to left knee arthritis. (Fig.1) She had a medical history of hypertension, diabetes mellitus, hyperlipidaemia, and rheumatoid arthritis. Preoperative spine x-rays showed an awkward fusion-like deformity of vertebral bodies (**Fig.2**) Preoperatively, bladder catheterisation demonstrated and orange colour of the urine (Fig.3). During the operation the knee cartilage and the menisci were black in colour and the surrounding soft tissues -especially the quadriceps and the patellar tendons - appeared an ink-like colour. (**Fig.4-7**) The surgeons realized that the patient had ochronosia. They also noticed black stains at the eye's sclera (**Fig.8**) and a blue-black discoloration of the ear cartilage (**Fig.9**). All above phenotypic manifestations set the diagnosis of alkaptonuria. A total knee arthroplasty was then performed **(Fig.10)**. Postoperatively, the patient was informed. The final diagnosis was set with the high levels of homogentisic acid in urine. We recommended the patient to seek for further genetic investigation.

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