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Case Report

Alkaptonuria

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Introduction

Alkaptonuria is a rare autosomal recessive (AR) metabolic disorder occurring due to deficiency of the enzyme homogentisate 1,2 dioxygenase which is involved in the metabolism of tyrosine. Deficiency of the enzyme results in binding of the oxidised polymers of homogentisic acid (HGA) to connective tissue and its excretion in the urine. Presence of homogentisic acid in urine is responsible for the characteristic black coloration of urine on standing, while its deposition in connective tissue leads to bluish green discoloration.¹

Case report

A 62-year old male patient was being evaluated for low back ache and pain in the knee joints. Clinical evaluation revealed presence of bluish discoloration of the auricular cartilages and diminished range of movements of the spine and the knee joints. Radiography of the spine revealed scoliosis of dorso-lumbar spine with osteopenia and wedge compression

of LV1 vertebra. There was widespread reduction of the intervertebral disc spaces with presence of discal calcification and vacuum phenomena at multiple levels. Marginal osteophytes were noted at multiple levels in the lumbar spine (Fig. 1). Radiographs of the pelvis and the knee revealed degenerative changes with joint space reduction (Fig. 2). Radiography also revealed calcification of the aural cartilage (Fig. 3). A CT of the spine was done which confirmed the findings on radiograph (Fig. 4). The patient's urine demonstrated dark pigmentation on standing. Based on the characteristic clinical and radiological findings, a presumptive diagnosis of Alkaptonuria was made.

Discussion

First described by Sir Archibald Garrod in 1908, Alkaptonuria is a rare autosomal recessive metabolic disorder with an estimated incidence of 1:250,000–1000,000. It has the distinction of being the first disease in which a Mendelian recessive inheritance pattern was proposed and described. It occurs due to the deficiency of homogentisate 1,2 dioxygenase, an enzyme responsible for the breakdown of the aromatic aminoacids phenylalanine and tyrosine.² Deficiency of this enzyme leads to excessive accumulation of HGA in the blood stream and its excretion in the urine. The disorder occurs worldwide, with the highest frequency seen in the Czech Republic where the prevalence approaches 1:25,000. There are isolated cases reported sporadically from India with the largest case series of seven cases reported by Parikh et al.³

The disorder is characterised by the triad of homogentisic aciduria, ochronosis and arthritis. The excessive accumulation of HGA leads to its excretion in the urine and is responsible for the urine turning dark on standing or on alkalinisation. Due to

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Fig. 1 – Radiograph of the dorso-lumbar spine showing osteopenia with scoliosis and wedge compression of LV1 vertebra. There is widespread reduction of the intervertebral disc spaces with presence of discal calcification.

Fig. 2 – Radiograph of the pelvis and knees, antero-posterior projection showing degenerative changes.

Fig. 3 – Radiograph showing calcification of the aural cartilage.

this affinity of homogentisic acid for alkalies it is called 'Alkapton' and the condition Alkaptonuria. This acid binds to collagen and accumulates in the connective tissue of the skin, cartilage, sclera and joints. The affected connective tissues become weak and brittle with time, leading to chronic inflammation, degeneration, and osteoarthritis (progressive arthropathy). While on gross examination the pigmentation of the connective tissue appears blue black, on microscopic examination it appears yellow (ochre) and therefore this pigmentation of the tissue is called 'Ochronosis'.⁴

Alkaptonuria though an inherited disorder may not manifest until the fourth decade when the degenerative joint disease starts manifesting itself. Ochronotic arthropathy, a manifestation of long-standing Alkaptonuria, occurs because of the accumulation of HGA in the joints. The most common radiological findings are noted in the spine where osteopenia is noted with dense disc calcification. The calcification involves the nucleus pulposus. The other conditions causing discal calcification include degenerative disc disease,

Fig. 4 – Sagittal reformatted CT of the spine showing the degenerative changes and the intervertebral disc calcification with vacuum phenomenon at multiple levels.

postoperative or post traumatic, ankylosing spondylitis, pseudogout, haemochromatosis, juvenile chronic arthritis, amyloidosis and hypervitaminosis D. In pseudogout, haemochromatosis and hypervitaminosis D the calcification involves the annulus fibrosus. The knee, hip and shoulder joints are the other commonly involved joints.⁵ The disorder may also involve the tendons, ligaments. Other systems can get involved. Ochronotic fibrosis of the costal cartilages may lead to a restrictive pulmonary disease while deposition of the pigment in the heart valves and coronary arteries may lead to calcification and stenosis of valves and vessels. There is also a generalised increased incidence of atherosclerosis and myocardial infarction is a common cause of death. The accumulation of HGA also predisposes a patient to developing renal calculi and associated complications of infection, obstruction and renal failure.⁶ Apart from plain radiography and CT,

ultrasonography may be useful in demonstrating enthesopathy, non-calcified fragments detached and embedded into the synovium, joint collections, small osteophytes and degenerative changes.⁷ Magnetic resonance imaging (MRI) has also been shown to be accurate in picking up early changes of ochronotic arthropathy⁸ such as ligamentous lesions, early changes in the intervertebral discs, which may not be demonstrable by conventional radiology.

The treatment of this condition remains ineffective. Dietary restriction of phenylalanine and tyrosine play a limited role in reducing the excretion of homogentisic acid and prevention of arthropathy. Nitisonone, a triketone herbicide and high-dose vitamin C (ascorbic acid) have been prescribed, but their efficacy has not been proven. Ochronotic arthropathy may require total joint replacement.

Conflicts of interest

The authors have none to declare.

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