ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

ALKAPTONURIC OCHRONOSIS AND ARTHROPATHY: A RARE CASE

DR.DEVAL PATEL, DR.PARTH PATEL, DR.JAGDISH PATWA, DR.HIMALI PATEL.
Department of pathology, S.B.K.S. Medical college and Research Institute, Vadodara, Gujarat.
Department of orthopaedics, S.B.K.S. Medical college and Research Institute, Vadodara, Gujarat

Manuscript Info

Manuscript History:

Received: 17 May 2015
Final Accepted: 22 June 2015
Published Online: July 2015

Key words:

Ochronosis, Alkaptonuria, Arthritis

Corresponding Author

DR.DEVAL PATEL

Abstract

Alkaptonuria is a rare autosomal recessive metabolic disorder resulting in a deficiency of homogentisic acid oxidase. Thus homogentisic acid accumulates in cells and body fluids and its oxidized polymers bind to collagen, leading to progressive deposition of grey to bluish black pigment resulting in degenerative changes in cartilage, intervertebral disc and other connective tissues, leading to arthritis which is the only disabling effect in an affected older individual. Alkaptonuria is a progressive disease and the three main features, according the chronology of appearance are: darkening of the urine at birth, then ochronosis(blue-black pigmentation of the connective tissue) clinically visible at around 30 years in the ear and eye, and finally a severe ochronotic arthropathy at around 50 years with spine and large joint involvements.

Copy Right, IJAR, 2015,. All rights reserved

INTRODUCTION

Alkaptonuria(AKU) is an extremely rare hereditary error of metabolism, transmitted as autosomal recessive trait which has an estimated incidence of 1:2,50,000 – 1:1,00,000.[1] This. Biologically characterized by the presence of homogentisic acid(HGA) in blood and urine. The urine darkens on standing in air and is characteristic of this disorder.[1] The presence of HGA is due to the deficiency of homogentisate 1,2 diaoxygenase, the third enzyme of the catabolic pathway of tyrosine in the liver and results from mutations in the corresponding gene.[2] Ochronosis is the deposition of an ochre coloured pigment within the skin, cartilage, collagenous tissues, heart endocardium, valves and kidneys as a result of alkaptonuria.[3] There is no known cure for this disorder and medical treatment is based on symptomatology. Due to its rarity in the prevalence rate, here we report a case of this rare metabolic disorder diagnosed and treated at our hospital wirh review of relevant literature.

Case History:

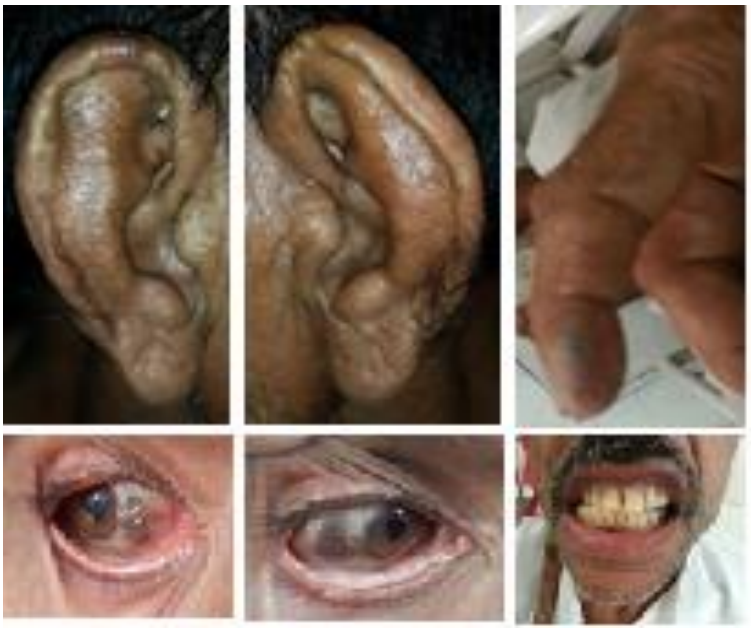
A 55 years old male patient, farmer by occupation came to our hospital with chief complaints of backache, pain over bilateral hip, knee, shoulder, elbow joints, unable to walk and difficulty to stand without support.

Patient had history of passing brownish black coloured urine on standing recognized at childhood due to spotting on the clothes and brownish black ear wax.

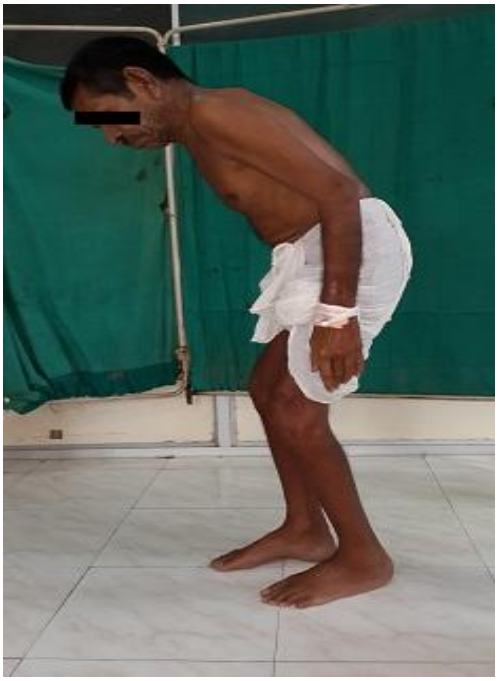
Back pain was insidious, mild, without tingling, numbness and radiation. Pain over bilateral hip region insidious, mild, radiating to knee joint and anteromedial aspect of thigh. Gradually patient developed difficulty in crossleg sitting, squatting and his daily routine work was hampered with restricted terminally painful movements. At bilateral shoulder and elbow mild restriction of movements and muscle spasm.

History of morning stiffness and generalized weakness. There was no history of same symptoms in his family.

General examination: Patient revealed pigmentation over ear. The ear cartilage was firm to hard in consistency. There was pigmentation of the skin over fingers, brownish black pigmentation on sclera, brown color pigmentation of the gums and teeth.(Figure 1) Chest expansion was only half centimeter.



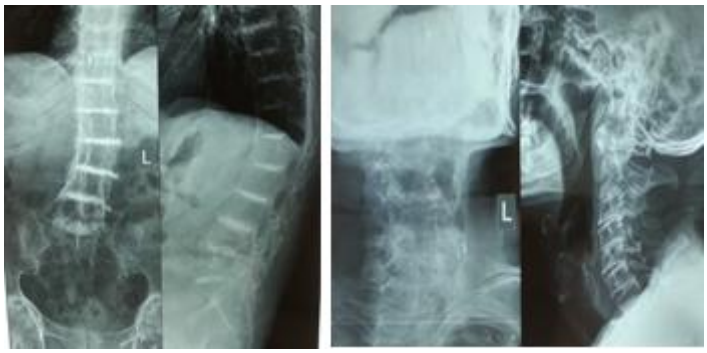
(Figure 1 : Pigmentation of the skin on ears and fingers, brownish black pigmentation on sclera, brown color pigmentation of the gums and teeth)



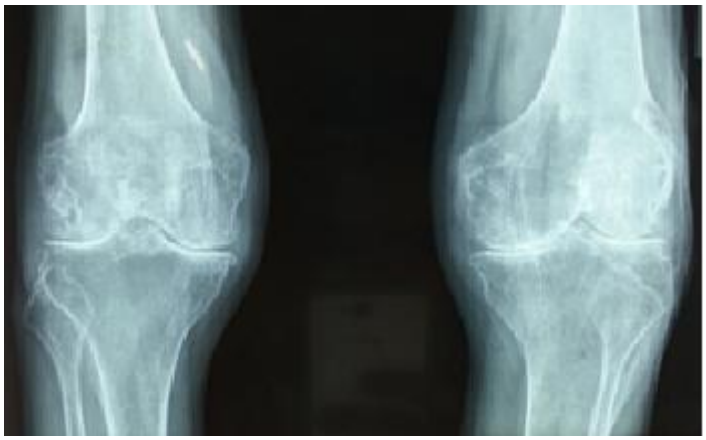
(Figure 2 :Dorsal kyphotic deformity of spine)

Spine revealed dorsal kyphotic deformity(Figure 2), paraspinal muscle spasm, tenderness over the lower thoracic, lumbar and cervical vertebras followed by restriction in movements. There was no neurological deficit. Flexion deformity at both the knee joints with limitation of range of movements. Range of motions at both the shoulder joints were limited.

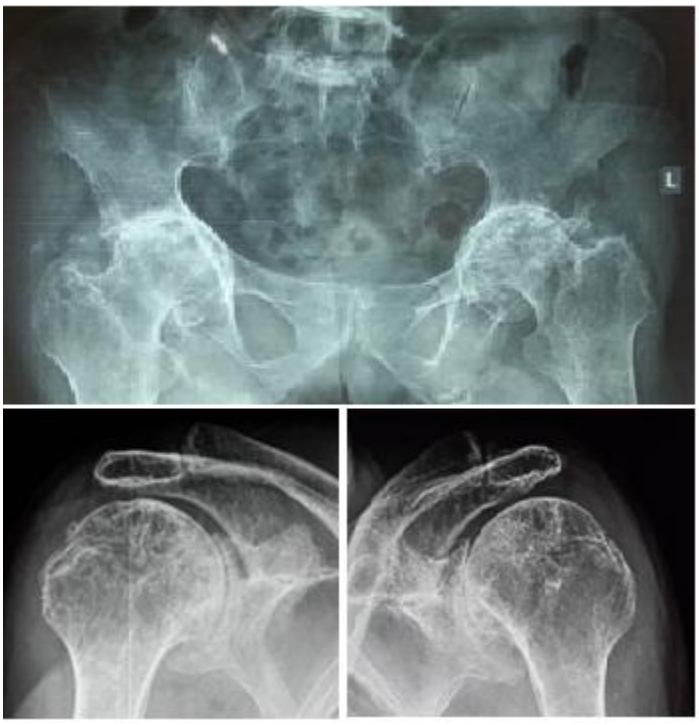
Roentgenography of dorsolumbar and cervical spine revealed calcification of the intervertebral disc spaces, thin wafer like disc spaces looking like a bamboo spine deformity.(Figure 3) X-ray of hip, knee and shoulder showed osteoarthrosis changes.(Figure 4,5).



(Figure 3: Calcification of the intervertebral disc spaces)



(Figure 4 : X-ray of knee showing osteoarthrosis changes)



(Figure 5 :X-ray of hip and shoulder showing osteoarthrosis changes)

Laboratory investigations:

Hb – 11.2 gm%, TC – 6980/mm3, DC –P – 64%, L – 27% , ESR – 20 mm/hr, RBS – 100 mg%, Blood urea – 16 mg%, Serum Creatinine – 1.1 mg%, Rheumatoid factor – Negative, ECG – Normal

Following biochemical tests were performed.

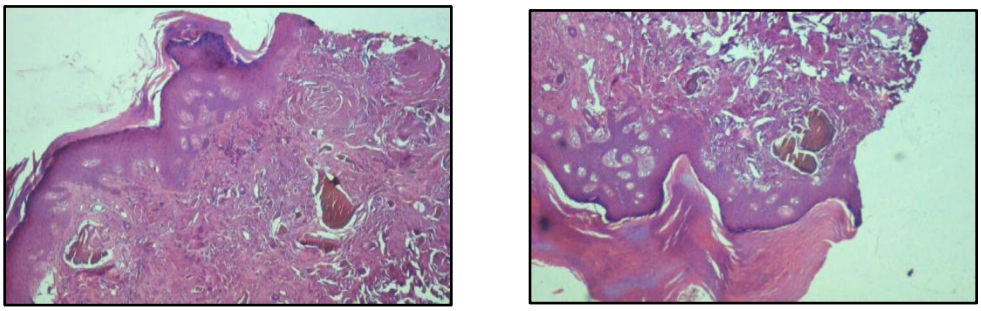
1. Urine turned black on exposure to air for many hours.(Figure 6)

(Figure 6 : Urine turns black colour on longstanding atmospheric exposure)

2. Ferric chloride test: transient green color formed.

3. Benedicts test: gave dark supernatant, initial greenish brown precipitate followed by a yellow precipitate of cuprous oxide on standing.

Histopathological examination of skin biopsy taken from the finger revealed hyperkeratosis of stratified squamous epithelium lining beneath which superficial reticular dermis shows yellow-orange colored pigment(Ochronotic pigment) within collagen bundles and swelling of collagen bundles.(Figure 7)



(Figure 7: Skin biopsy showing Ochronotic pigment within collagen bundles and swelling of collagen bundles)

Overall features based on clinical, radiological, biochemical and histopathological investigations are consistent with clinical diagnosis of Alkaptonuria ochronosis.

Treatment: Patient was treated symptomatically with analgesics, muscle relaxants, physiotherapy, multivitamins and Vitamin C 500mg daily, patient was advised to take Vitamin C rich and restricted protein diets. Currently the patient is asymptomatic and is under follow up every six months at our hospital.

Discussion:

The urine of an alkaptonuric individual usually appears normal when passed. However, it starts to darken upon standing. This is caused by oxidation and polymerization of the homogentisic acid, and it is enhanced with an alkaline pH. Therefore, an acidic urine may not become dark even after many hours of standing. This is one of the reasons why darkening of the urine may perhaps never be noted in an affected person, and the diagnosis may be delayed until adulthood, when arthritis or ochronosis occurs. This gradual change in urine color often is a premonitory sign of alkaptonuria.

Generally, there are two different forms of ochronosis. Exogenous ochronosis is a chemical syndrome that results from prolonged exposure to certain chemicals such as hydroquinone, phenolic compounds, benzene substances, and oral antimalarials which can lead to the abnormal deposition of blue-black pigment in the skin only.[4] Endogenous ochronosis is a result of alkaptonuria.

Clinical ochronosis is the second stage of the disease and appears around 20-30 yrs of age. Ochronosis affects several connective tissues with variable frequencies. The ears(~70%), which present as a bluish discoloration of the pinna. The eyes(~50%) with brown sclera pigmentation. The other tissue could be affected with a smaller frequency(5-10%): hands, nose with bluish discoloration and gum, teeths with a brown tinge.[1] Tendons may also be involved, frequently observed as discolouration over the knuckles.

Ochronotic arthropathy is the third stage of the disease and usually appears during the fourth decade of life. It begins with dorsolumbar spine involvement: lower back pain and stiffness due to articular cartilage degeneration with bone remodelling, disc calcifications, porotic vertebral bodies and joint spaces narrowing. This condition is quite similar to osteoarthritis.[5] Involvement of large joints like knees, shoulders and hips usually occurs several years later. The course is chronic, progressive and leads to disability and crippling that needs to often undergo surgical replacement.

Several therapeutically approaches have been used in AKU patients with little success. Current treatments are usually palliative. They are treated by low tyrosine intake i.e. low protein diet, analgesic drugs, physiotherapy, muscle relaxants and/or rest.[6] Homogentisic acid inhibits the growth of cultured human articular chondrocytes, and binds to connective tissue in rats.[7] Ascorbic acid prevents these effects. Recent advance showed administration of Nitisinone[8] and further work is going on gene or enyme replacement by liver transplantation or gene therapy.[9]

However, the average life span of the patient is unchanged and they die of causes comparable with the general population.[10]

References:

1.O'Brain WM, La Du BN, Bunim JJ: Biochemical, pathologic, and clinical aspects of alkaptonuria, ochronosis and ochronotic arthropathy: Review of world literature. Am J Med 1963; 34:813-38.
2.La Du B N, Zanoni V G, Laster L & Seegmiller J E(1958). J Biol Chem 230,251-260.
3.Casselman F, Herijigers P, Meyns B, Daenen W. Aortic stenosis in endogenous ochronosis. J Heart Valve Dis. 1999;8:445-446.
4.Garcia SF, Egbert B, Swetter SM. Hereditary ochronosis: hyperpigmented skin overlying cartilaginous structures. Cutis. 1999;63:337-338.
5.Lagier R (2006) Rheumatol Int 26, 361-364
6.Aquaron R, Rodriguez de Cordoba S, Penalva M, Badens C& Roux H (2009) Curr Rheumatol Rev 5, 111-125
7.Stoner R, Blivairs BB. Homogentisic acid metabolism: a 1, 4 addition reaction to benzoquinone -1 acid with amino acids and other biological amines. Fed Proc 1965; 24: 656.
8.Introne W J, Perry M B, Troendle J, TsilouE, Kayser M A, Suwannarat P et al.(2011) Mol Genet Metab 103, 307-314
9.Ranganath L R, Jarvis C J & Gallagher J A (2013) J Clin Pathol 66, 367-373
10.Parikh A, Khubchandani RP, Bharucha BA, Kumta NB, Pandya MB, Naik G. Alkaptonuria-a series of seven cases. J Assoc Physicians India 1988;36:565-6.