IJPMR October 2007; 18 (2): 54-57 *Case Report*

Rehabilitation of a Patient with Alkaptonuric (Ochronotic) Arthritis

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Abstract

A 54-year old male presented with chronic low back pain without radiation and significant early morning stiffness of 10 years duration and pain in both knees for the last 5 years. History revealed black staining of innerwear (brief) following micturation since childhood. On physical examination, kyphoscoliosis, paraspinal muscle imbalance, restriction of the ROM of lumbosacral spine, knee tenderness and pigmentation of ear and sclera were found. Radiologic features like narrowing of disc space with disc calcification and fusion of disc in lumbosacral segment, osteoarthritis of knee pointed towards the diagnosis and biochemical finding of positive urinary homogentisic acid confirmed the diagnosis of alkaptonuric (ochronotic) arthritis. Prophylactic dose of ascorbate was started. Initially NSAID and later acetaminophen were used for pain control. Spinal orthosis was given and therapeutic exercise programme instituted. Analgesic use was significantly reduced after 3 months. VAS (pain) score, WOMAC score, hand to floor distance, 50 feet walk time, Patient & Physician Global Assessment etc. were used to monitor LBP and knee pain. All the outcome measurement tools showed significant improvement at 3, 6, 9 and 12 months. Patient's work place fitness also improved significantly as measured by the number of sick leaves per month.

KEY WORDS: **Alkaptonuric arthritis; Ochronosis; Homogentisic acid; Disc calcification; Ascorbate; Therapeutic exercise.**

Introduction

Alkaptonuria (MIM 203500) is a rare metabolic disease characterized by a triad of homogentisic aciduria, arthritis and ochronosis[1]. It is a rare metabolic disorder first described by Garrod[2]. The worldwide incidence is 1:250000[3]. The disease is notably frequent in Czechoslovakia where the incidence approaches 1:25000[4]. There are very few cases reported from India[5]. The disease is caused by mutations in the homogentisate 1,2 dioxygenase (HGD) gene and deficiency of the enzyme. This leads to accumulation of homogentisic acid, an intermediate metabolite of phenylalanine and tyrosine catabolism[6]. Ochronosis occurs because of the deposition of a melanin-like brownish black pigment, derived from the oxidised product of homogentisic acid in the connective tissues and cartilage. Genetically, alkaptonuria is inherited as an autosomal recessive trait[7]. Recently, alkaptonuria gene was assigned to human chromosome 3q 21-q23.

In 1996, Fernandez-Canon et al. cloned the gene for homogentisate 1,2 dioxygenase (HGD, EC 1.13.11.5), and they demonstrated that HGD harbors the mutation that co-segregates with the disease and provided biochemical evidence that at least one of these missense mutations is a loss of function mutation[6].

The urine of an alkaptonuric individual usually appears normal when passed. However, it starts to darken upon standing due to oxidation and polymerization of the homogentisic acid. Alkaptonuric patients are usually asymptomatic as children or young adults[8-10]. When they get older, pigmentation of the sclera or the cartilage of the ear start to appear. Pigmentation may be seen in the teeth[11], buccal mucosa, and in the nails or the skin, giving these areas a dusty coloration. The widespread deposition

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of pigment in alkaptonuric patients is called ochronosis[12,13], a term used to describe the darkening of tissues, which is due to a slow accumulation of the black polymer of homogentisic acid in the cartilage and other mesenchymal tissues.

Arthritis is the only disabling effect of this condition, and occurs in almost all patients with advancing age[14,15]. The earliest symptoms are usually in the hips, spine and knees, the large weight-bearing joints. The arthritis has the clinical characteristics of rheumatoid arthritis; however, the radiological picture is of severe osteoarthritis (OA). In contrast to osteoarthritis, the large joints at the hip and shoulder are most commonly involved, whereas the sacroiliac joint may be spared. The degenerative changes in the lumbar spine are quite characteristic, with narrowing of joint spaces and fusion of vertebral bodies, resulting in marked limitations of motion with ultimate ankylosis. Ochronotic arthropathy in the hips and the knees may be so severe as to require total joint arthroplasty[16]. The disease is more severe in men, although the incidence in the two sexes is equal[18].

There is a high incidence of heart disease[18], commonly due to mitral and aortic valvulitis. Secondary calcification of the aortic valve may be so severe as to necessitate urgent aortic valve replacement[19]. Ischemic heart disease with ultimate myocardial infarction is a common cause of death.

Case Report

A 54 year male patient presented with low back pain (LBP) without radiation and with early morning stiffness (EMS) of approximately 30 minutes for the last 4 years. Pain exacerbated after pelvic traction received outside. He also complained of bilateral knee pain for 5 years and painful limitation of right shoulder of 6 months duration.

History revealed LBP without EMS for 19 years. On enquiry he revealed the history of black staining of innerwear (brief) since childhood (Fig.1). There was no history of drug intake like quinacrine or application of cream containing hydroquinone. Family history was not contributory. There was no history of consanguinity.

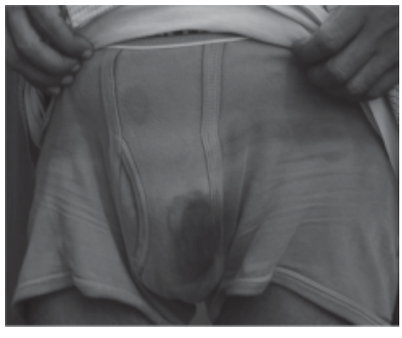

Fig 1: Staining of Innerwear. Black staining of brief is noticed.

Pigmentation of sclera and pinna were noted, on examination (Fig.2). Kyphoscoliosis with paraspinal muscle imbalance and restriction of ROM LS spine and right shoulder were detected. Both knees were tender.

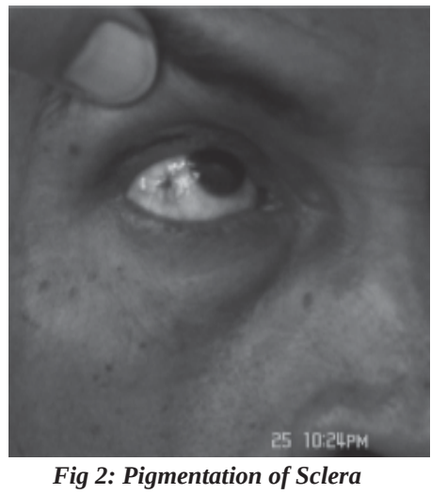

Fig 2: Pigmentation of Sclera Pigmentation seen in both eyes.

Radiological investigations of lumbosacral (LS) spine showed disc space narrowing, disc calcification, fusion of disc and "Bamboo- like spine" appearance, along with kyphoscoliosis (Fig.3A,B). X- rays of dorsal spine revealed mild scoliosis with convexity to right and disc calcification. Radiology of both knees detected osteoarthritic changes while that of right shoulder did not point to any OA changes. No loose body was found in knee, hip or shoulder.

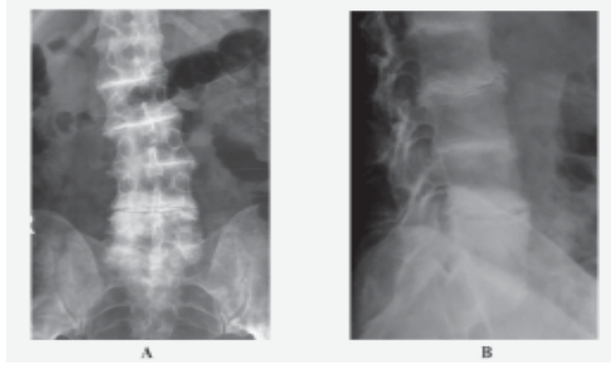

Fig 3: "Bamboo- like spine" A: Anteroposterior view of lumbosacral spine showing disc space narrowing, disc calcification, fusion of disc and scoliosis.B: Lateral view also showing straightening of spine.

Ecocardiography was performed. However, no aortic dilatation, aortic or mitral valve calcification, or aortic or mitral valve regurgitation were detected. Concentric left ventricular hypertrophy was seen.

Ultra-sonography of the KUB showed prostatomegaly with thick bladder wall, but any renal or prostatic stone was not detected.

Urinary homogentisic acid excretion was estimated as 1.91 mmol per mmol of creatinine. Other haematological and biochemical investigations were within normal limits.

Pharmacologic Interventions: Initially NSAID and later acetaminophen were used for pain control. Muscle relaxant was also used. Ascorbate was started at a dose of 500 mg/day to slow the rate of oxidation of homogentisic acid.

Non-pharmacologic Interventions: Moulded spinal orthosis (semi-rigid type) was given. Therapeutic exercise programme instituted for kyphoscoliosis and knee osteoarthritis included therapeutic spinal exercise programme, ROM exercise knee, multiple angle isometric & isotonic strengthening exercises for knee, ROM exercise shoulder and ROM exercise hip. Shoulder mobilization exercise was also prescribed for concomitant periarthritis of right shoulder.

Outcome: Analgesic use was significantly reduced after 3 months and no analgesic was required after 9 months. VAS (pain) score, VAS (stiffness) score, hand to floor distance were used to monitor low back pain and the improvement of the knee was assessed using VAS (pain), WOMAC score, 50 feet walk time. Patient Global Assessment and Physician Global Assessment were also assessed. All the outcome measurement tools showed significant improvement in both LBP and knee pain at 3, 6, 9 and 12 months after institution of rehabilitation programme (Table 1). Also in Schober's test, pretreatment value of 2 cm changed to post treatment value of 3.5 cm. Patient's work place fitness also improved significantly as the number of sick leaves per month over a period of 3 months dropped down from 2.33 to nil after 1 year of treatment.

Discussion

Diagnosis of the case is clearly evident from the typical history, characteristic triad, radiological & biochemical features. Though the patient also complained of EMS and X-ray showed "Bamboo-like-spine", EMS duration of less than 1 hour along with normal values of ESR & CRP, uninvolved SI joints and normal chest expansion point towards noninflammatory LBP. EMS can be attributed to ankylosis and kyphoscoliosis.

Patient developed urinary retention during management period and the prostatomegaly detected by USG corroborates with that.

Concentric left ventricular hypertrophy found in echocardiography was probably due to the concomitant hypertension.

According to the literature homogentisic acid production may be reduced by low- protein, low- phenylalanine, and low- tyrosine diet. But, there seems to be no demand for such a restricting diet to deal with an arthritis, which begins only in adult life and progresses slowly over many years[20]. Evidences suggest nitisinone effectively reduced urinary HGA levels in patients with alkaptonuria. But, long-term clinical trials to determine the benefits of nitisinone in preventing joint deterioration and providing pain relief, and to determine its long-term side effects are yet to be planned[20,21]. Ascorbic acid may slow the rate of oxidation of homogentisic acid to pigment precursors[20]. So, the selected pharmacologic agents addressing the basic metabolic derangement were based on evidences. Also the role of spinal orthosis and specific therapeutic exercises in this clinical setting is well supported by literatures.

Conclusions

Treatment of arthritis involves both pharmacological and nonpharmacological approaches[22]. Thus our approach of rehabilitative management of a patient with arthritis associated with inborn error of metabolism, comprising of ascorbate, symptom- relieving drugs, therapeutic exercises and orthosis seems to be justified according to evidence and proved to be fruitful in this case according to outcome. The case is presented due to rarity of the condition in the Indian settings.

Acknowledgement

We are thankful to Dr. Shiuli Roy (Adak), Dept. of Biochemistry, IPGMER and Dr. Tanusree Das, IICB for their generous help.

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