CASE REPORT

ALKAPTONURIC OCHRONOSIS : REPORT OF A CASE AND BRIEF REVIEW

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ABSTRACT

Alkaptonuria, a metabolic disorder characterized by a triad of homogentisic aciduria, arthritis and ochronosis is one of the first conditions in the charter of group of inborn errors of metabolism proposed to have Mendelian recessive inheritance. It is due to the deficiency of the enzyme homogentisic acid oxidase which catalyzes the conversion of homogentisic acid to maleylacetoacetic acid in the catabolism of tyrosine. Homogentisic acid thus 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. However the diagnosis can be made in neonates when blackish stain is noticed in an unwashed diaper. Alkaptonuria is treated symptomatically, surgical intervention necessitates in advanced stages, treatment with ascorbic acid (Vitamin C) and dietary restrictions of food containing phenylalanine and tyrosine have proved to be successful in alleviating the symptoms.

KEY WORDS

Ochronosis, Alkaptonuria, Ochronotic arthritis

INTRODUCTION

Ochronosis in other terms called as Alkaptonuria (AKU) arises from the Arabic word alkapton for "alkali" and Greek word "to suck up oxygen greedily in alkali" based on the observation that the urine becomes black on standing when it becomes alkaline. This disorder is of considerable historical interest in that it was one of the original "inborn errors of metabolism" described. At the turn of the 20th century, Archibald Garrod, a pediatrician, recognized that the syndrome, which has been called AKU, showed a pattern of familial inheritance. It was proposed that AKU and certain other disorders were due to genetic defects, each of which resulted in the lack of activity of a particular metabolic enzyme. Forty five years later, it was confirmed that the biochemical defect in AKU is a lack of

homogentisate oxidase in the tyrosine catabolic pathway. This disorder occurs in about 1 in 2,50,000 births. Due to its rarity in the prevalence rate, we report this case of AKU who was diagnosed and treated at J.J.M. Medical College and Hospital, Davangere and we discuss the clinical aspect, laboratory investigations and management of this condition along with a brief review of relevant literature.

CASE REPORT

A 45 year old female admitted with a history of back pain, stiffness of the back, generalized weakness for the last one and half month.

The backache was insidious in onset and progressive in nature associated with early morning stiffness, she was not able to get up from the sitting position without the support, she had occasional tingling sensation of the limbs. She also complained of pain in both knee joints. She had no other constitutional symptoms. She had undergone tubectomy 15 years back and hysterectomy 5 years back.

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Fig. 1A

Fig. 1B

Fig. 1C

Fig. 1D

Fig. 1A & 1B: Pictures showing pigmentation of the ear cartilage, concha and anthelix.

Fig. 1C: Pigmentation of conjunctiva in the interpalpabral fissure

Fig. 1D: Pigmentation of gums and teeth

General examination of the patient revealed pigmentation of the ear cartilage, concha and anthelix (Fig. 1A & 1B), pigmentation of the conjunctiva on both eyes in the interpalpabral fissures (Fig. 1C), brown colour pigmentation of the gums and teeth (Fig 1D). She had impaired hearing of both the ears.

Local examination of the spines revealed dorsal kyphotic deformity, paraspinal muscle spasm and there was tenderness over the lower thoracic and lumbar vertebrae followed by

restricted movements. There were no neurological deficits.

Roentgenographic findings : a routine dorsolumbar spine X-Ray revealed calcification of the intervertebral disc-spaces looking like a bamboo spine deformity and osteoarthritis of knee and hip joints (Fig. 2).

Fig. 2 : X-rays showing calcification of intervertebral disc-spaces having bamboo spine deformity. Osteoarthritis of knee and hip joints.

Laboratory investigations: were as follows :

Hb – 10.2 g%, TC – 7,400, DC – P – 61%, L – 32%, ESR – 17 mm/hr, RBS – 90 mg%, Blood Urea – 15mg%, Serum Creatinine – 0.9 mg%, ECG – Normal

Though routine laboratory investigations were normal, taking into consideration general examination, local examination and radiological findings AKU was suspected and to confirm the diagnosis, following biochemical tests were performed.

1. Urine turned black on exposure to air for many hours.
2. Ferric chloride test: transient green color formed.
3. Ammoniacal silver nitrate test: black precipitate of silver formed.

4. Benedicts test: gave dark supernatant, initial greenish brown precipitate followed by a yellow precipitate of cuprous oxide on standing.
5. N-butanol test: pinkish brown color developed.

Based on clinical and radiological evaluation and biochemical investigations AKU was diagnosed.

Treatment: Patient was treated symptomatically with analgesics and physiotherapy and was given Vitamin C 500mg daily, patient was advised to take Vitamin C rich diets. Currently the patient is asymptomatic and is under follow up every six months in the out patient clinic of the hospital.

REVIEW OF LITERATURE

AKU, a metabolic disorder characterized by a triad of homogentisic aciduria, arthritis and ochronosis enjoys the historic distinction of being one of the first conditions in which Mendelian recessive inheritance was proposed and is also one of the conditions in the charter of group of inborn errors of metabolism (1). AKU or the excretion of urine which darkens on exposure to air, is an autosomal recessive disorder due to deficiency of homogentisic acid oxidase, which catalyzes the conversion of homogentisic acid to maleylaceto acetic acid. (2). Homogentisic acid accumulates in cells and body fluids. Its oxidized polymers bind to collagen, leading to the progressive deposition of grey to bluish black pigment (3). Cartilage apparently has a special affinity for homogentisic pigment and when sufficient amounts are aggregated within the articular plates, there is death of the chondrocytes and calcification of cartilage (4,5). Alkaptonuric patients are usually, asymptomatic as children or young adults, when the affected individuals get older, pigmentation of the sclera or the cartilage of the ear start to appear (6). Pigmentation may be seen in the teeth (7), buccal mucosa and in the nails or the skin, giving these areas a dusty coloration. Arthritis is the only disabling effect of this condition, and occurs in almost all patients with advancing age (8, 9). The screening tests like fehling's or Benedicts could be confirmed by measurement of homogentisic acid and its derivative benzoquinone acetic acid by enzymatic spectrophotometry (10) or by using gas liquid chromatography (11) or by high pressure liquid chromatography (12).

Genetically, AKU is inherited as an autosomal recessive trait (13). Janocha et al (14) demonstrated linkage to microsatellite markers from proximal 3q. Markers on that chromosome were selected for study because of previously demonstrated homology of syntenic with mouse chromosome 16 (15).

Independently, Pollak et al (16) used homozygosity mapping to locate the alkaptonuric gene to 3q 2 in a 16 CM region. Sucrase-isomaltase deficiency (17) and neonatal hyperparathyroidism (18) could be co-inherited with AKU. 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 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 (19).

Homogentisic acid inhibits the growth of cultured human articular chondrocytes, and binds to connective tissue in rats (20). Ascorbic acid prevents these effects. Wolff et al treated two adult patients with high doses of ascorbic acid. The level of excretion of homogentisic acid did not change, whereas its derivative, benzoquinone acetic acid, completely disappeared from the urine (13).

AKU a metabolic disorder, though not life threatening, disability and pain forms the major complaint of these patients. General examination, local examination and radiological examination followed by biochemical tests help in confirming the diagnosis. Osteoarthritis can be treated symptomatically as for other osteoarthritis. Surgical intervention necessitates in advanced stages. Treatment with ascorbic acid (Vit. C) and dietary restrictions of food containing phenylalanine and tyrosine have proved to be successful in alleviating the symptoms.

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