A case of alkaptonuria

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Alkaptonuria was one of four disorders originally defined as an "inborn error of metabolism" by Garrod in 1902. It is a rare autosomal recessive disorder, characterized by the triad of homogentisic acid in urine, ochronosis and arthropathy.

We describe an elderly female who presented with ochronotic pigmentation and was found to have Alkaptonuria.

Case report

A 52 year old female presented with a history of progressive low backache for 7 years and painful swelling of right knee for 6 months, to the orthopaedic clinic. She was referred to the dermatology department at North Colombo Teaching Hospital, Ragama regarding bluish pigmentation of palms and soles for 12 years. There was no history of handling chemicals or dyes. There was no family history of similar illness and there was no parental consanguinity.

On examination her sclerae were bluish with blackish macules medial to cornea in both eyes (Fig 1). Ears were thickened and stiff. Close to the borders of the palms and soles bluish hyperkeratotic multiple macules with irregular outline were present. Bluish tinge was present also in her nails. Examination of the locomotor system revealed diminished movements of lumbar spine and painful restricted movements of right knee. No abnormalities were found in cardiovascular, respiratory and nervous systems. Abdominal examination was normal.

The white cell count, blood urea, serum electrolytes, serum creatinine, and fasting blood sugar levels were normal. However her Benedict's test was positive. Urine became reddish brown upon contact wih air for a few hours. With addition of NaOH it became black. Same colour change was noticed on adding an equal volume of AgNO3. Urine became red when 2 drops of FeC13 were added. These findings indicated the presence of homogentisic acid (HGA) in her urine sample.

X-ray of thoraco lumbar spine showed generalized osteoporosis, calcification of intervertebral discs and narrowing of disc spaces. X-ray of the right knee joint showed severe osteoarthritic changes, with evidence of joint space narrowing and sclerosis of articular surfaces. These radiological appearances were compatible with severe degenerative changes for her age.

Histology of skin showed hyperkeratosis and acanthosis of epidermis with brown pigment deposited on dermal collagen (Fig 2). There was no evidence of a naevous or a cellular reaction around this pigment.

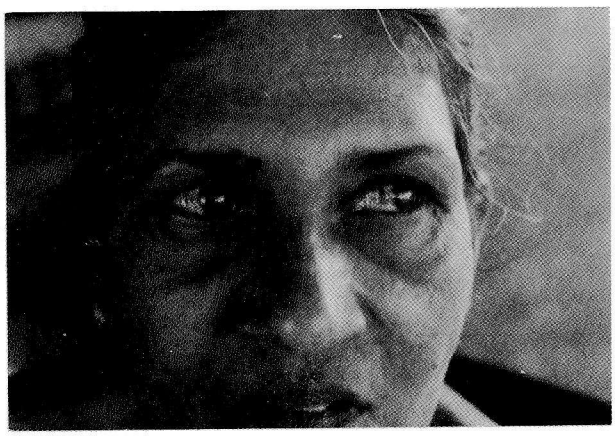

Figure 1. Ochronotic scleral pigmentation.

Figure 2. Ochronotic pigment in dermal collagen.

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Discussion

This patient presented with ochronotic pigmentation. Ochronotic pigmentation can be exogenous[1]. It is known to be induced by hydroquinone, phenol, trinitrophenol and benzene. This patient had no history of contact with such agents. In addition, exogenous ochronosis is not accompanied by arthropathy or homogentisic acid in urine. Investigations revealed homogentisic acid in urine confirming the diagnosis of alkaptonuria.

Alkaptonuria is due to the deficiency of enzyme, homogentisic acid oxidase that leads to accumulation of HGA in tissues and excretion of HGA in urine. It is an autosomal recessive disorder. The gene coding for this enzyme is found to be located in chromosome 3q[2].

The highest incidence of alkaptonuria is found in Czechoslovakia and Santa Domingo where there is significant inbreeding. Incidence in Sri Lanka is not known. There are two publications in Sri Lankan medical literature about this disease[3,4].

In cartilage and connective tissues, homogentisic acid is deposited as benzoquinon acetic acid. This is also known as 'ochronotic pigment'. This binds irreversibly to tissue collagen inhibiting collagen cross-linking leading to diminution of its integrity. This results in early degeneration and calcification of cartilage.

The earliest sign of the disorder is dark urine noted in napkins in infancy. Black cerumen and perifollicular axillary pigmentation may be noted before the age of ten. Scleral pigmentaion occurring between corneal margin and inner canthus is seen as early as third decade. Ochronotic pigmentation can also be detected on the nasal tip, cheeks, costochondral junctions, superficial tendons, fingernails and buccal mucosa. In the fourth decade the onset of thickening and blue black dicoloration of ear cartilage is evident.

Insidious progression of arthropathy begins in the fourth decade in males and about ten years later in females. Accelerated artherosclerosis is common in the older age group. There is significantly increased incidence of myocardial infarction in these patients. Inspite of all these disabilities it is considerd as a benign disease with normal life expectancy.

Increased levels of homogentisic acid in urine is determined by simple urinary studies. Specific identification and quantification of HGA can be done by spectrophotometric methods. A screening test with NaOH impregnated filter paper is useful for field studies.

At present no effective medical treatment is available for alkaptonuria. Administration of vitamin C upto 1g per day is recommended for older children and adults. The antioxidant nature of ascorbic acid helps to retard the deposition of HGA in tissues. Reduction of dietary phenylalanine and tyrosine reduces homogetisic acid production and maybe helpful if started in early life. Ochronotic arthropathy is managed with physiotherapy, analgesics, rest and prosthetic joint replacement. Exogenous cutaneous ochronosis has been treated with carbon dioxide laser and dermabrasion.

In a murine model of alkaptonuria, a compound known as methyl trifluoro benzoyl cyclohexandione (MTBC) was shown to be a potent inhibitor of the enzyme which catalyses the formation of homogentisic acid in the body. Development of this compound may result in the first potent pharmacotherapeutic agent for the treatment of this metabolic disorder.

References

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