ALKAPTONURIA - BLACK URINE DISEASE

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ABSTRACT

BACKGROUND

Alkaptonuria is a rare inborn error of metabolism inherited as an autosomal recessive disease. Homogentisic acid, an intermediate product in the metabolism of phenylalanine and tyrosine cannot be further metabolised due to constitutional lack of enzyme Homogentisic acid oxidase. The metabolic defect causes a characteristic triad – homogentisic aciduria, ochronosis and arthritis. We present a case of a 9-year-old boy born to a non-consanguineous couple who presented to the outpatient department, with parents c/o of urine turning black on long standing. Similar complaint is seen in his younger brother of age 3 years. No significant family history. General and systemic examination showed no abnormality. Tests for reducing substances were positive. Thin layer chromatography was positive for homogentisic acid. Homogentisic acid, the intermediate product accumulates in blood and tissues. Homogentisic acid and its oxidised form allkapton are excreted in urine, giving it an unusually dark colour. The accumulating homogentisic acid causes damage to cartilage called as ochronosis leading to osteoarthritis. Pigmentation may be noted in the cartilage of ear, sclera and corneal limbus of eye. Complications in the old age include valvular heart disease and renal calculi. Ochronosis is prevented by reducing homogentisic acid accumulation, achieved by dietary restriction of phenylalanine and tyrosine. Enzyme replacement is the definitive treatment.

KEYWORDS

Homogentisic Acid, Ochronosis, Phenylalanine, Tyrosine and Thin Layer Chromatography.


BACKGROUND

Alkaptonuria is a rare, hereditary, metabolic disease in which the enzyme homogentisic acid oxidase is missing. Because of this defect, homogentisic acid produced during the metabolism of phenylalanine and tyrosine cannot be further metabolised; instead it accumulates and is excreted in urine. It is characterised by the triad of homogentisic aciduria, ochronosis and arthritis. It was also one of the four inborn errors of metabolism described by Garrod in his Croonian lectures of 1908. This disorder occurs in about 1 in 2,50,000 births. Due to its rarity in the prevalence rate, we report this case of alkaptonuria in a 9-year-old boy who presented at our outpatient department.

CASE REPORT

A 9-year-old boy born to a non-consanguineous couple, of lower socioeconomic status, presented to the outpatient department with parents c/o urine turning cola (Black) colour on long standing since the age of 1 year. No h/o discolouration of skin or joint pains. Similar complaints have been noted in his 3-year-old brother. There was no other medical problem in the family. Childhood growth and development was normal.

General physical examination showed no pigmentation of the sclera and ear lobe cartilage, gait was normal. Systemic examination (including joint examination) revealed no abnormality.

Biochemical tests were done to assess presence of homogentisic acid in urine i) urine appeared pale yellow at the time of collection (Fig. 1) but on prolonged exposure to the atmosphere, it turned dark brown to black colour (Fig. 2); ii) Benedict’s test and ferric chloride test for reducing substances were positive; iii) thin layer chromatography was positive for homogentisic acid (Fig. 3). Radiological examination showed no degenerative changes in lumbar spine, knee and hip joint.

Based on the history and examination, a diagnosis of alkaptonuria was made. In the above case, dietary restriction of proteins, ascorbic acid supplementation, regular followup for early detection of complications in later age was advised.

Figure 1. Urine at the Time of Collection
DISCUSSION

Alkaptonuria was designated by Sir Edward Garrod as the first inherited metabolic disease. Alkaptonuria or the excretion of urine which darkens on exposure to air is an autosomal recessive disorder due to deficiency of homogentisic acid oxidase, an important enzyme in the catabolism of aromatic amino acids. It catalyses the conversion of homogentisic acid to maleylacetoacetic acid, which is ultimately converted to fumaric and acetoacetic acid. There are good reasons for thinking that alkaptonuria is not the manifestation of a disease but is rather of the nature of an alternative course of metabolism, harmless and usually congenital and lifelong. Witness is borne to its harmlessness by those who have manifested the peculiarity without any apparent detriment to health from infancy on into adult and even advanced life. Alkaptonuric individuals on a normal diet void urine that at first is not an abnormal colour and that may not darken for many hours if it remains at an acid pH. This is true even for patients with extreme ochronosis. Two factors that favour rapid darkening are the excretion of alkaline urine and a lower concentration than normal of vitamin C and possibly other reducing agents that are usually present in urine. It is well known that vitamin C protects homogentisic acid against oxidation; and in the past, vit. C was suggested as a therapeutic agent because of this property.

Most of the diagnostic tests for alkaptonuria by urinalysis are based on the detection of homogentisic acid through its unusual properties. Paper or thin layer chromatography of urine directly is a simple technique to identify homogentisic acid. Rapid analysis of homogentisic acid in urine and plasma is possible using HPLC method. A stable isotope dilution mass spectrometry method also permits measurement of homogentisic acid.

Alkaptonuric patients are usually asymptomatic as children or young adults. With advancing age ochronosis i.e. pigmentation of sclera, ear cartilage start to appear. “ochronotic arthritis” is a regular manifestation of longstanding alkaptonuria. It appears that this feature is more severe in males than in females. Other complications include high incidence of heart disease, ruptured intervertebral discs, prostatitis and renal stones.

Severe dietary restriction of phenylalanine and tyrosine is not practical except for brief periods. Sealock et al have pointed out that increased tissue concentrations of ascorbic acid might prevent the deposition of ochronotic pigment, even though this treatment does not alter the basic metabolic defect. The definitive treatment is replacement of the missing enzyme. This will be made possible in the future with the application of genetic engineering.

REFERENCES