Original Research Paper

Volume -10 | Issue - 3 | March - 2020 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Biochemistry

ALKAPTONURIA-- A CASE REPORT OF RARE DISEASE

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ABSTRACT Alkaptonuria also known as Black Bone Disease or Black urine disease is a rare autosomal recessive disorder. It was first described by Archibald Garrod as an inborn error of metabolism in 1902 in London.(4).The problem is in tyrosine metabolism in the liver due to deficiency of homogentisinate 1,2 dioxygenase (HGD).Which results in accumulation of homogentisic acid (HGA) in the cells and body fluids. The 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 This is the main disabling effect seen in later life. The diagnosis can be made in neonates and infancy when blackish stain is noticed in an unchanged diaper. The classical triad is that of that of homogentisic aciduria, arthritis and ochronosis. Treatment of Alkaptonuria is mainly symptomatic. Ascorbic acid (Vit C) and dietary restriction of foods containing phenylalanine and tyrosine is recommended. Surgical intervention may be required at a later date in advanced stages. The disease is very common in Dominion Republic and Slovakia.

KEYWORDS : Alkaptonuria, ochronosis, homogentisic acid

INTRODUCTION

Alkaptonuria is due to deficiency of homogentisate1, 2 dioxygenase also known as homogentisic acid oxidase (HO).Homogentisic acid oxidase is required in the metabolism of phenyl alanine and tyrosine during the step when homogentisic acid (HA) is converted to maleyl acetoacetate Due to the deficiency of HO ,HA accumulates and is oxidized to benzoqinone acetate which rapidly polymerizes. The urine darkens on exposure due to oxidation of HA. Late in the disease there is arthritis and connective tissue pigmentation due to the binding of the oxidized polymer (1).This pigmentation is called ochronosis. The pigment can be found in the sclera, conjunctiva, limbic cornea, cardiac valve (aortic valve mainly),intervertebral disc, muscles and other tissues, Fatal complications may occur in older age(2,3)

Case presentation

We are presenting two case reports of alkaptonuria diagnosed at our Pediatric department.

Case no. 1

Two and half year old female child was brought by parents with history of blackish discoloration of diapers after passing urine and black staining of bed sheet in the morning .Mother first noticed this when baby was two months old. The baby was otherwise normal and healthy. She was the first issue, born of a non-consanguineous marriage. The baby was delivered at home. There was no history of antenatal, intranatal and postnatal problem. She was exclusively breast fed and immunized appropriate for age . Physical and systemic examination revealed no abnormality. White diaper changed to black stain few hours after discharge of urine.

Examination of the baby revealed an active and alert baby weighing - 14 kgs, height 93 cms ,head circumference of 46 cms Examination of eyes including fundus , the musculoskeletal systems, skin, and cardiovascular system was normal. Qualitative urine examination showed dark greenish black discoloration due to presence of homogentisic acid in a voided urine sample (Figs.3.) Quantitative examination of urine revealed concentration of homogentisic acid level to be 905.12 mg/dl (normally HA is not present in urine).

Examination of eyes, musculoskeletal system, skin and cardiovascular system was normal. Ultrasonography abdomen revealed multiple bilateral renal calculi mild cystitis, eye exam was normal Patient is being treated symptomatically with Vitamin C 100 mgs and has been advised to take Vitamin C rich diets. Parents have been counseled to avoid foods rich in tyrosine and phenyl alanine, This includes products like milk, meat, poultry, egg, cheese, and nuts.

Case no,2

Six months old male infant presented with history of blackish discoloration of diapers after passing urine and black staining of bed sheet in the morning .Mother first noticed this when baby was one month old, Clinical examination of the infant was essentially within normal limits.He was the second issue ,born out of non consanguineous marriage in our hospital. This baby was exclusively breast fed.Physical and systemic examination was essentially within normal limits. On examination weight was 5 kgs, length 66 cms, head circumference 42 cms.Other general and systemic examination was essentially within normal limits Examination of urine showed dark greenish black discoloration due to presence of homogentisic acid. (Figs.3.) Concentration of homogentisic acid in urine was 1460 mg/dl (normally HA is not present in urine).

Fig.1.Fresh urine and same urine after few hours

Fig.2.Staining of the diaper bed sheet

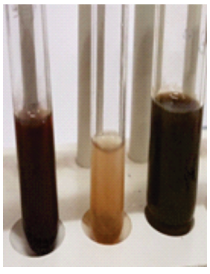

Fig.3.Ammoniacal silver nitrate test

DISCUSSION

Alkaptonuria also known as ochronosis is one of the original inborn errors of metabolism described by a famous pediatrician Dr Archibald Garrod in 1902.(3).He commented that Alkaptonuria shared a pattern of familial inheritance.It is an autosomal recessive disorder. Pollak et al. mapped the alkaptonuria gene to the chromosome 3q2.La Du et al in 1958 identified the deficient enzyme. (1).

The deficiency in Alkaptonuria is that of homogentisic acid oxidase in liver and kidney leading to excessive accumulation of homogentisic acid, an immediate metabolite of phenylalanine, and tyrosine metabolism (5,7). As homogentisic acid accumulates both intracellularly and extracellularly, it is oxidized to benzoquinone acetate, which polymerizes to form melanin-like polymer, resulting in deposition of polymer, a dark yellow pigment or 'ochre' occurs in the cartilage and other connective tissue.(5)

Earliest symptom of alkaptonuria is darkening of the urine on standing (as a result of oxidation and polymerization of homogentisic acid). Dark urine stains on the diaper are sometimes the first sign of the disease in infants Darkening of urine is the only feature suggestive of alkaptonuria in the pediatric age group in most patients. (8)Apart from the above phenomenon, the patient usually remains asymptomatic until third or fourth decade. (8)

Pigmentation of sclera is the first sign to appear, commonest sign being insertion of lateral rectus muscle (Osler's sign) and this usually starts around third decade. (5,8) Skin pigmentation becomes more obvious in fourth decade. Ear cartilage involving concha, antihelix, and tragus in that order (ochronosis) is one of the first sites to be affected. (9) The discoloration tends to be most pronounced on sun-exposed sites, cartilage of the ears and nose, areas of high eccrine sweat gland density, such as axillae, palms soles, and genitalia. (5) There may be bluish discoloration of mucosae tendons, especially dorsum of hands, nail bed and crown half of the teeth. Tendons also may show similar discoloration and it is demonstrated by making a fist, upon which, there is discoloration of the extensor tendons over the knuckles. (8) A heavy deposition in the larynx, trachea and bronchi, esophagus may result in hoarseness and dysphagia, (10) involvement of tympanic membrane and ossicles may cause tinnitus and deafness. (5,9) Abnormal pigmentation of kidneys and prostate, heart valves, endocardium, aortic intima, coronaries, and rarely, aortic calcification and pigmented prostatic calculi have been observed on surgical procedures. (11)

Ochronotic arthropathy is a particularly troublesome feature and appears around the fourth decade. There is involvement of weight-bearing joints like spine and knees as well as shoulders, with narrowing of joint spaces and calcifications. Arthritis is the only disabling effect of this condition and occurs in almost all patients as the age advances. (5,8,9)

The diagnosis is confirmed by the identification and quantification of homogentisic acid in urine using gas liquid chromatography. The levels of homogentisic acid are increased in the blood, urine, and tissues. Screening for mutations is done after extracting the genomic DNA from whole blood and subjecting it to PCR. (5,6,12)

Active surveillance for cardiac, renal, and prostate complications should be done after the fourth decade. (5) No effective therapy is available for the treatment of alkaptonuria at present. Dietary restriction of phenylalanine and tyrosine play a limited role in reducing the excretion of homogentisic acid. Foods to be avoided include milk, meat, poultry, egg, cheese, and nuts. Diet may prevent further progression of arthropathy.

Homogentisic acid inhibits the growth of cultured human articular chondrocytes and binds to connective tissue, Ascorbic acid prevents these effects.(14). Vitamin C (ascorbic acid), homogentisic acid and can reduce the tissue damage, but its efficacy has not been proven. (5,8)

Nitisinone, a triketone herbicide, has shown to significantly reduce the excretion of homogentisic acid by inhibiting the enzyme 4-hydroxy phenylpyruvate dioxygenase that is responsible for the synthesis of homogentisic (1,8,13) acid. (1,8,13).Long term studies are needed regarding its safety and efficacy. Supportive therapy like NSAIDs and physical therapy is used for arthropathy in later life.

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