Early detection of alkaptonuria

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ABSTRACT

Alkaptonuria is a rare disorder of metabolism characterized by deficiency of homogentisic acid oxidase. This leads to the characteristic features like darkening of urine, ochronosis and arthropathy. Darkening of urine is one of the first symptoms noticed by the parents of the child suffering from this disorder. Ochronosis is seen in various organs like eyes, skin, tendons and joints. A case of 10 year old boy is reported who was brought to this clinic with the presenting complaint of bluish discoloration of sclerae. This discoloration led to eliciting positive history of dark urine off and on. Further investigations confirmed alkaptonuria.

Keywords: Alkaptonuria, Blue sclerae, Ochronosis

INTRODUCTION

Alkaptonuria is a rare metabolic disease and is caused by deficiency of the enzyme homogentisic acid oxidase. It is characterized by ochronosis, the process of brownish black pigmentation of eyes, skin, joints and some vital organs like heart and kidneys. The condition commonly presents in adulthood. However, we came across a 10 year old boy who presented with pigmentation in the eyes.

CASE REPORT

A 10-year-old boy was brought to this clinic by his parents who were concerned about the changing color of his eyes, which were turning bluish black since the past 18 months. Careful inquiry revealed that they had noticed very dark urine puddles at times on the periphery of their Asian style toilet.
and consistency. There was no history of discoloration of sweat. There was no joint pain, swelling or deformity. X-rays of the hip, spine and knees were normal. There was nothing to suggest a cardiac problem. ECG and echocardiogram were normal. The child was otherwise normal. All growth milestones were normal. The patient was a product of a second-degree consanguineous marriage. There was no family history of similar complaints. The child had phimosis, which made him dribble and spray urine outside the Asian style toilet, which used to stay at the periphery and change color at times. There was no history of any drug intake including in the recent past.

The parents were instructed to bring back urine that had been freshly voided by the child. They brought back urine that was black in color. They said that it was normal in color when the child was voiding it but changed its color after about an hour of standing. This was sent to the lab for detection of homogentisic acid. Liquid gas chromatography showed high amount of homogentisic acid.

A diagnosis of alkaptonuria was made on the basis of the bluish black discoloration of the sclera, black-colored urine upon standing and detection of homogentisic acid in the urine. The patient was referred to a pediatrician who put him on 500 mg of ascorbic acid twice daily orally and a low-protein diet. The patient will be followed up on a four-monthly basis.

DISCUSSION

Alkaptonuria is a very rare disease. (About 1:250,000). It has the distinction of being the first disease in which a Mendelian recessive inheritance pattern was proposed. It is also one of the first diseases described under the heading of ‘Inborn errors of metabolism’.

The disease is the result of a deficiency of homogentisic acid oxidase, which is an important enzyme in the catabolism of aromatic amino acids. This deficiency prevents the breakdown of homogentisic acid finally to fumaric and acetoacetic acid. There is a build up of oxidized and polymerized homogentisic acid throughout the body, more so in fibrous and cartilaginous tissue. This in turn leads to a brownish black melanin-like pigmentation, a phenomenon known as ochronosis.

One of the first symptoms of alkaptonuria is darkening of the urine upon standing. However, the urine is of normal color when fresh. This phenomenon is due to oxidation and polymerization of homogentisic acid. It is also pH-dependent and hence in some patients of alkaptonuria it is never seen if their urine has an acidic pH. Dark urine stains on the diaper are sometimes the first telltale sign of the disease in infants. Darkening of the urine is the only feature suggestive of alkaptonuria in the pediatric age group in most patients.

Apart from the above phenomenon, the patient is usually asymptomatic until the third or fourth decade. Other main features of the disease include ochronosis and arthropathy. There is bluish black or grayish blue pigmentation of the outer ocular tissues like the sclera and cornea and conjunctiva. Scleral pigmentation (Osler’s sign) starts around the third decade. In our case it started at the age of 10 years and that was the presenting feature of the disease, which is unusual.

Skin pigmentation usually appears around the fourth decade. One of the first sites to be involved is the ear cartilage, which becomes thickened with bluish black pigmentation. Eyelids and forehead too show pigmentation. Tendons show similar discoloration and it is demonstrated by telling the patient to make a fist upon which there is discoloration of the extensor tendons over the knuckles. There may be widespread dusky discoloration of the skin of the cheeks, forehead, axillae, and genitalia. The buccal mucosa and larynx can be discolored too. Nails can be stained brown.

Other systems can also be involved. There may be signs of aortic or mitral valvulitis. There may be prostatic or kidney stones.

Ochronotic arthropathy is a particularly troublesome feature and appears insidiously around the fourth decade resembling osteoarthritis. There is involvement of weight-bearing joints like the spine and
knees as well as shoulders.

Detecting and measuring the amount of homogentisic acid in the urine confirms the diagnosis of this disease. This is done by enzymatic spectrophotometry or gas liquid chromatography.[11,12]

Treatment of alkaptonuria is frustrating. It involves giving a low-protein diet with restriction of phenylalanine and tyrosine. However, this is not a very practical measure. Ascorbic acid is given in the dose of 500 mg BID to reduce connective tissue damage. Presumably, the ascorbic acid with its antioxidant property helps to retard the process of conversion of homogentisate to polymeric material that is deposited in cartilaginous tissues.[3,13] Supportive therapy like NSAIDs and physical therapy is used for the arthropathy. Unfortunately, the course of the disease remains the same. However, the average life span of the patient is unchanged and they die of causes comparable with the general population.[1,3,5]

This case of alkaptonuria is unique for its presentation at such a young age. The patient’s parents noticed the bluish black pigmentation of the sclera at the age of about 10 years. This is distinctly unusual considering the fact that the usual age for scleral pigmentation is around the third decade. The patient’s black-colored urine was discovered per chance by the parents because he used to dribble due to his phimosis, and it turned black upon standing on the side of the Asian toilet where spillage and dribbling occurs more commonly than in a Western style commode. Liquid gas chromatography clinched the diagnosis.

**REFERENCES**