CASE REPORT

CEREBRO-SPINAL AND RENAL OCHRONOSIS : A RARE CASE REPORT

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ABSTRACT

Alkaptonuria, a rare inborn error of tyrosine metabolism, characterized by the absence of homogentisic acid oxidase results in the accumulation of homogentisic acid in the body. Associated renal failure and cerebral infarction is rare and usually occurs in the later stages of the disease. We report a 55-year-old male who presented, initially with features of stroke and degenerative arthritis. He had pigmentation of sclerae, darkening of urine on long standing, abnormal renal profile, degenerative arthritis and cerebral infarction. Alkaptonuria was suspected and biochemical tests confirmed mild renal impairment, homogentisic acid in urine and homogentisic acid crystal was detected cytologically in urine sediment. Such a case of Alkaptonuric ochronosis with cerebrovascular and renal complications have been rarely reported in the previous literature.

KEY WORDS

Alkaptonuria, Homogentisic acid, Stroke, Renal failure, Ochronosis.

INTRODUCTION

Alkaptonuria (AKU) is a rare inborn error of metabolism of amino acid tyrosine, caused by deficiency of the enzyme, homogentisic acid oxidase (HGA) in the liver and kidneys. It affects one in 2,50,000 to one million people worldwide, which is inherited as a recessive Mendelian trait. It was also one of the four inborn errors of metabolism described by Garrod in his croonian lectures of 1908. The gene responsible for the disorder has been localized to chromosome 3q (1). It is characterized by a triad of homogentisic aciduria, arthritis and ochronosis. Although alkaptonuric arthritis, cardiac and spinal manifestations are common, not much clinical cases are reported about cerebrovascular and renal complications of AKU (2). We report an undiagnosed case of alkaptonuric ochronosis with rare clinical presentation as central nervous

system (cerebrovascular and spinal) and renal complications on which not much clinical cases are reported (3). Here we discuss the clinical manifestations of this rare disorder with a review of the relevant literature.

CASE REPORT

A 55 year old male patient had complaints of weakness of right upper and lower limb, fixed flexion deformity of right hip joint and aphasia since 3 days and severe pain in the large joints since 15 years. General examination revealed black pigmentation of sclera in right eye (Fig 1). Examination of joints revealed arthritis in both knee joints, fixed flexion deformity on right hip joint. Percussion tenderness was positive over the lumbar spine with marked limitation of movements. Lasegue's test was positive and movements at both the hip

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Fig 1: Black pigmentation (less marked) in sclera of right eye

Fig 2A: X-ray of thoraco- lumbar region showing osteoporosis and symmetrical reduction of disc space with calcification

joints were limited and painful. Radiological study revealed kyphosis in thoraco- lumbar region with osteoporosis and symmetrical reduction of disc space with calcification (Fig 2A), symmetrical reduction of glenohumoral joint (Fig 2B), complete osteolysis of head and neck of right femur with upper displacement of shaft and symmetrical reduction of left hip joint space (Fig 2C). Central nervous system examination showed impaired reading and writing, poor comprehension, right sided upper motor neuron type facial palsy, brisk reflexes

Fig 2B: X-Ray of right shoulder joint showing symmetrical reduction of glenohumoral joint

Fig 2C: X-Ray of hip joints showing complete osteolysis of left femur with upper displacement and symmetrical reduction of right hip joint space

in right upper limb and right ankle with intact sensations. No signs of meningeal irritation. CT-Scan Brain (plain) revealed subacute to chronic infarct in anterior and left middle cerebral arteries (Fig 2D). Laboratory investigations revealed normal blood and lipid profile, euglycemia, normal liver function, but mildly raised blood urea (42.3mg%) and serum creatinine (1.8 mg%). Urine turned black (cola coloured) on exposure to air for many hours. Ammonical silver nitrate test showed brown-black precipitate (Fig 3A). Benedict's test showed initial

Fig 2D: CT-Scan (plain) of brain showing subacute to chronic infarction in the territories of anterior and middle cerebral arteries

Fig 3: A-Silver nitrate test, B-Benedict's test, C-Ferric chloride test

greenish precipitate followed by a yellow precipitate of cuprous oxide (Fig 3B). With ferric chloride test transient blue-green colour was formed (Fig 3C). In this case, the urinary HGA levels were 14.2 mmol/mol creatinine.

Cytological study of urine sediment in this case on haematoxylin-eosin staining demonstrated large pigmented crystal surrounded by few bacilli and lymphocytes (Fig 4).

DISCUSSION

AKU occurs due to deficiency of HGA oxidase which catalyzes the conversion of HGA (also called alkaptone) to maleyl acetoacetate, fumaric acid and acetoacetic acid. Persons homozygous for defective AKU alleles cannot carry out the breakdown of HGA, which accumulates in the blood and is then excreted in the urine (3). In patients with AKU, HGA polyphenol oxidase, catalyzes the oxidation of the accumulated HGA in vivo to benzoquinone acetate, an ochronotic pigment that has a high affinity for joints, spinal disks, bones, cardiac valves and dura mater. This oxidation occurs spontaneously

Fig 4: Homogentisic acid crystal on Haematoxylin-Eosin staining-low power microscope

in urine, where the environment is alkaline and aerobic (4). Ochronosis occurs in tissues due to long exposure to HGA. Dense, coal-black pigmentation of costal, tracheal and laryngeal cartilages, blue-grey pigmentation of the ears and sclera (osler's sign), and extensive early degenerative arthritis of the spine and large joints (due to the breakdown of the cartilage-pigment complexes) — are the result of this pigment deposition (5). In the present case, scleral pigmentation in right eye was seen. But there were no pigmentations in skin or cartilages. Degenerative arthritis, disk space narrowing and disk calcifications observed in the dorsolumbar spine X-Ray and degenerative arthritis in large joints on X-Ray confirmed ochronosis.

Alkaptonuric patients have dark urine or urine that turns dark when left standing, and excrete >4-8 g/day of HGA. The kidney eliminates the huge HGA load produced in the body by glomerular filtration and tubular secretion. The diagnosis of alkaptonuria is made by demonstrating homogentisic aciduria and is confirmed by enzymatic spectrophotometry, gas liquid chromatography or high pressure liquid chromatography (6). Our patient noticed urinary discoloration first and we could not find any other cause of pigmenturia including drugs, porphyrin, bilirubin and amorphous urates, except HGA (7). Screening the urine of patient's close relatives was negative for homogentisic acid. Urine turned black (cola coloured) on exposure to air for many hours. HGA is a reducing agent and was detected by: silver nitrate test (brown-black precipitate),

Benedict's test (initial greenish precipitate followed by a yellow precipitate of cuprous oxide) and ferric chloride test (transient blue-green colour). HGA was elevated in 24-hr urine by spectrophotometric analysis (8, 9). The normal urinary HGA levels are less than 11 mmol/mol creatinine (10). In this case, the urinary HGA levels were 14.2 mmol/mol creatinine.

Cardiac manifestations include aortic or mitral valvulitis, formation of atherosclerotic plaques containing cholesterol and fat, calcification of the coronary arteries and eventually myocardial infarction (11). However, in our case no cardiac manifestations were detected. Cerebral involvement is usually rare not much cases are reported, although spinal involvement has been previously reported (12). CT-Scan reveals stroke in the present case.

Laboratory investigation revealed mildly increase blood urea and serum creatinine levels. We also detected large pigmented HGA crystal with mild infective focus by cytology of urine sediment on haematoxylin-eosin staining which is rarely reported in AKU patients. But ultrasound examination of abdomen was normal. This suggested mild obstructive renal failure which can in later stages of AKU. Pigment deposits form stones in the prostate, kidneys and urethra probably because of the extremely high levels of urinary HGA excretion (13). Based on clinical, biochemical tests and radiological findings alkaptonuric ochronosis was diagnosed but renal and cerebrospinal complications were coincidental. However, we could not get any laboratory evidence relating AKU with stroke.

Low protein diet (low in phenylalanine and tyrosine) in combination with ascorbic acid, Nitrofurantoin (a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase which decreases the excretion of HGA), AKU gene replacement therapy, joint / valvular replacement therapy, renal transplantation for renal failure and physiotherapy and rehabilitation procedures in later stages for neurological involvement - are several therapeutic approaches that have been used in patients with AKU (14, 15).

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