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A CASE REPORT OF ALKAPTONURIA

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Abstract : Alkaptonuria is a one of the inborn errors of metabolism characterized by triad of homogentisic aciduria, arthritis and ochronosis. It is due to the defect in the homogentisic acid oxidase gene located on human chromosome 3q21-q23, results in a defect in the metabolism of homogentisic acid. The diagnosis was made with history of darkening of urine on prolonged standing and positive ferric chloride test. Here we report a case of alkaptonuria with lumbar spine involvement.

Keyword : Alkaptonuria, Homogentisic acid, ferric chloride test.

CASE REPORT

A 61 years old male patient, known to have diabetes mellitus for past 10 years under regular treatment presented to the orthopaedic department with complaints of severe pain in the right knee joint and lower back for the past one month. History of darkening of urine on prolonged standing present. No history of trauma or fever. No family history of similar complaints. On examination CVS, RS, CNS and Abdomen systems are normal.

BP- 140/90 mmHg, PR- 70/mint, RR- 22/mint. General physical examination shows black pigmentation of sclera. Local examination on spine - shows diminished lumbar lardosis. Local examination of right knee joint – swelling present. Fine needle aspiration of right knee joint - shows black cloloured fluid. X ray Lumbar spine - showed the evidence of fused vertebral segments with intervertebral disc calcification.

Lab investigations: Urine routine

- Albumin - +
- Sugar - +
- Acetone – negative
- Bile – negative
- WBC/HPF – negative
- RBC/HPF – 1-2
- Epithelial cells/HPF – 1-2
- Random blood sugar – 182 mg/dl
- Urea – 24 mg/dl
- Creatinine – 0.92 mg/dl

From the history, alkaptonuria suspected and following investigations were done to confirm the diagnosis.

i. Urine became black colour on exposure to air for few hours. Blackening started to appear from the top layer.

ii. Urine Benedict's test: positive

Procedure: To 5ml of Benedict's reagent in a test tube, add 8 drops of urine and mix well. Boil carefully over a flame for 2 minutes.

Observation: yellow precipitate is obtained. Colour changed to black after few hours. Benedict's reagent: It contains copper sulphate, sodium carbonate and sodium citrate. Urine glucostix test was negative that ruled out glucosuria.

iii. Urine Ferric chloride test: positive

Procedure: Adding a drop of Ferric chloride to the little amount of urine.

Observation: Bluish green colour is obtained.

Based on the above biochemical investigations, the diagnosis of alkaptonuria was made.

Treatment

Explained the condition and its prognosis to that patient. The extent of this patient's lumbar disease had necessitated a lumbar discectomy. Suggestion to undergo spine surgery (L4,L5 Discectomy) for his present situation.

DISCUSSION

Alkaptonuria is a rare metabolic disorder first described by Sir Archibald Edward Garrod. He first used the expression, "Inborn errors of metabolism" to describe four rare disorders, Alkaptonuria, Albinism, Cystinuria and Pentosuria. He discovered that such disorders resulted from enzymatic defects in the catabolic pathways of aminoacids and sugars.1 Alkaptonuria is characterized by triad of homogentisic aciduria, arthritis and ochronosis. It has the historic distinction of one of the first conditions in which mendelian recessive inheritance was proposed and is also one of the conditions in the charter of group of inborn errors of metabolism.2 Autosomal recessive mutations of the homogentisic acid oxidase gene located on human chromosome 3q21-q23, results in a defect in the metabolism of homogentisic acid.1 The homogentisic acid oxidase (HGD) gene provides instructions for making an enzyme called homogentisate oxidase. This enzyme helps break down homogentisate into maleyl acetoacetate. Mutations in the HGD gene impair the enzyme's role in this process. As a result, homogentisate accumulates in the body.3 The disease is more severe in men, although the incidence in the two sexes is equal. The urine of an alkaptonuric individual usually appears normal when passed. However, it starts to darken upon standing. This is caused by oxidation and polymerization of the homogentisic acid, and it is enhanced with an alkaline pH. Therefore, acidic urine may not become dark even after many hours of standing. This is one of the reasons why darkening of the urine may perhaps never be noted in an affected person,

and the diagnosis may be delayed until adulthood, when arthritis or ochronosis occurs.2 The most common clinical manifestations of ochronosis involve the skeletal, respiratory, cardiovascular, genitourinary, cutaneous and ocular systems.4 Generally these clinical manifestations are not evident until around the fourth decade of life because there is insufficient pigment deposition within affected tissues.5

In the skeletal system, cartilaginous deposition of pigment results in brittleness and fragmentation of these structures. While the exact mechanism of these pathologic changes is unknown, it is thought to be due to the pigment acting as a chemical irritant that inhibits the cartilage' s metabolic enzyme system.6 consequently arthritis is the most common clinical feature of ochronosis.7 Ochronotic spondyloarthropathy shows a gradually progressive course. The changes result from the deposition of the ochronotic pigment within the articular cartilages. With the loss of elasticity, the cartilages become brittle, they develop calcification and they later break down, leading to secondary degenerative changes.

The dorsolumbar spine is commonly affected8 and it shows reduced intervertebral disc spaces, a dense disc calcification (a wafer like calcification) and the vacuum phenomenon, with relatively little osteophytic changes. The annulus fibrosis gets calcified first followed by the nucleus pulposis in the late stages. Osteopenia is also noted. With ochronosis, degenerative changes may be seen throughout the entirety of the vertebral column, resulting in generalised pain and stiffness.9A spontaneous vertebral fusion with ankylosis can occur in the later stages. The hip and the knee joints show reduced joint spaces with subchondral sclerosis and cystic changes.

The increasing disc calcification and the associated vacuum phenomenon with minimal osteophytic changes are the specific imaging findings of alkaptonuria.10 A variety of cardiovascular abnormalities are associated with the deposition of pigment in the cardio vascular system. A thorough preoperative evaluation of the patient's cardio vascular status is essential. The cardio vascular lesions of ochronosis include discolouration of heart valves, endocardium and intima of the aorta. Heart valves can also become calcified and stenotic. These valvular changes are due to accumulation of pigment and donot occur until middle age. The aortic valve has the highest incidence of calcifications and stenosis, followed by the mitral and pulmonary valves. There is also an increased incidence of generalised atherosclerosis, and myocardial infarction is a common cause of death.7 Ochronosis results in the pigment deposition in the cartilage associated with the respiratory system and it causes the cartilage to fragment and become brittle. These pathologic cartilaginous changes often result in xerostomia and dyspnoea. Heavy deposition of pigment in the laryngeal, tracheal and bronchial cartilages may result in hoarseness and dysphagia. Restrictive pulmonary disease also may result from ochronotic fibrosis of the costal cartilages. This patient did not manifest any of the potential respiratory problems associated with alkaptonuric ochronosis.4 The alkapton urine has a high propensity for stone formation. Very rarely alkaptonuria patients end up into renal failure and the renal biopsy reveals a diffuse chronic tubulo-interstitial disease characterized by extensive tubular atrophy, interstitial fibrosis, inflammation and the deposition of the melanin like pigment in the tubular cells and the interstitium. The formation of calculi is secondary to the accumulation of homogentisic acid in the body which precipitates the deposition of crystals and formation of calculi.

The composition of prostatic and renal calculi is usually the standard calculus constituents such as calcium oxalate monohydrate and dehydrates, hydroxy apatite, beta calcium phosphate and osto calcium phosphate. The prostatic calculi may have substituted calcite Ca (Mg,Mn)Co3.1 The discolouration evident in the skin is due to deposition of ochronotic pigment within the hair follicles and sweat glands. With age, the blue-black discolouration appears, particularly in the external ears, sclera, oral mucosa, nails, skin and air exposed cutaneous sites. Pigmentation is rarely observed before the age of 20 or 30 years. Ocular pigmentation is especially prominent and appears in approximately 70% of the patients. Referred to as the Osler sign, ochronotic pigment deposition is confined to the exposed areas of the sclera and becomes evident during the third decade of life. Up to our knowledge, there is no literature to suggest that scleral pigment deposition is associated with any effects on visual function.7 The disease is usually first suspected after parents notice a child's urine turning dark when exposed to air. Homogentisic acid is a strong reducing agent that produces a positive reaction with Benedict and Ferric chloride reagent. Gas chromatography can detect traces of homogentisic acid in the urine.

The diagnosis could also be confirmed by the high-pressure liquid chromatography method for the quantitation of homogentisic acid and its derivative benzoquinone acetic acid. Measurement of this product by this method is used for therapy monitoring. DNA testing can look for the mutated HGD gene. Family history is very useful in making a diagnosis of alkaptonuria. However, many people do not know they carry the gene.2 Several therapeutic options are proposed to treat patients with alkaptonuria. Large doses of ascorbic acid (vitamin c) may slow down the accumulation of pigment in the cartilage. This could slow the development of arthritis. Dietary protein (contains phenyl alanine) restriction advised to reduce the amino acid levels. Some foods that contain phenyl alanine include: meats, milk products, soy, nuts & seeds, many types of artificial sweeteners. Reducing phenyl alanine in the diet has been shown to reduce the levels of homogentisic acid in children. Evidence is less clear in adults. However, Dietary protein restriction and high doses of ascorbic acid to reduce urinary homogentisic acid levels did not prove effective. Nitisinone, a triketone herbicide, inhibits 4-hydroxy phenyl pyruvate dioxygenase, an enzyme which produces homogentisic acid in the tyrosine metabolism. This is the only drug that has a proven efficacy in reducing the urinary levels of homogentisic acid but the long term safety profile needs to be studied.1 Non-dietary treatments for alkaptonuria are focused on preventing possible complications. These include arthritis, kidney stones and heart diseases.

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