Case Report

ALKAPTONURIA – CASE REPORT AND REVIEW OF LITERATURE

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SUMMARY

Alkaptonuria (AKU) is an important inborn error of metabolism. A documented case in a Pakistani family is being reported. The study concludes that Alkaptonuria (AKU) does occur in Pakistan.

KEYWORDS: Alkaptonuria, Homogentisic acid, urine chromatography, inborn errors of metabolism.

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INTRODUCTION

ALKAPTONURIA (AKU) is a rare inherited genetic disorder of tyrosine metabolism characterized by the triad of homogentisicaciduria, ochronosis and arthritis. It is one of the conditions in which Mendelian recessive inheritance was proposed.[1] It was also one of the four inborn errors of metabolism described by *Garrod* in his croonian lectures of 1908.[2] The clinical manifestations are that urine turns dark on standing and on alkalization due to elimination of excessive amounts of homogentisic acid (HGA), blue-black pigmentation of connective tissues and cartilages and arthritis of weight bearing joints.[3]

Frequency: The condition is rare, affecting one in 250,000 to one million people worldwide.[3] In US, the incidence is 1 case per 4 million populations.[3] This disease is unusually common in Slovakia (where incidence is 1 in 19,000)[4] and Dominican Republic.[5] Cases have also been reported from UK, Germany, Lebanon, Sudan, Saudi Arabia, Turkey and other parts of the world.[6,7]

We report a Pakistani family with two alkaptonuric children - referred to Mayo Hospital, Lahore, Pakistan for detailed study where they were thoroughly investigated, diagnosed and prescribed treatment. Hereby we discuss the clinical manifestations and management of this rare disorder with a review of the relevant literature.

CASE REPORT

A female infant of one-month age d/o a non-consanguineous couple, noted by the parents to have darkening of the clothes, diapers and napkins moistened with urine when left unwashed for many hours. She has a six year old sister with the same complaint; other siblings (two brothers and one sister) were normal. There was no other medical problem in the family. Childhood growth and development of the elder case was normal. Physical examination revealed no abnormality. There was no pigmentation of the sclera and ear lobe cartilage. Joint examinations were normal. The urine of both the cases appeared normal on collection but it turned dark brown to black on prolonged exposure to the atmosphere. Routine laboratory investigations were normal and radiological examination (of the elder girl)

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showed no degenerative changes in the knee and hip joints and the lumbar spine. The paper and thin layer chromatography and photometry revealed the presence of heavy amounts of HGA in the urine. Both of them were prescribed ascorbic acid (500mg BD) and low protein diet. Currently both of them are asymptomatic. After screening the close family members, no other case was detected.

DISCUSSION

AKU is an autosomal recessive disorder due to deficiency of homogentisic acid oxidase (HGAO) which catalyzes the conversion of HGA (also called alkaptone) to maleyl acetoacetate, fumaric acid and acetoacetic acid.[3] In the absence of the enzyme HGAO, homogentisic acid and benzoquinone acetic acid (BQA)[3,8,9] builds up in the body. (See Figure-1). Some is eliminated in the urine and rest is deposited in the connective tissues where it is toxic and is harmful to the bones and the cartilages.[8,9]

Homogentisic acid is itself colorless in the solution but is readily oxidized to a series of brown and black pigments on exposure to the air especially in the presence of alkali.

The fresh urine of an alkaptonuric appears normal but starts darkening on exposure to the air. This is caused by oxidation and polymerization of the HGA and speeds up on alkalization.[3,10] Hence, (strongly) acidic urine may not darken for many hours on standing. This may be one of the reasons why darkening of the urine may not be noted in an affected child and the diagnosis is delayed until adulthood when arthritis or ochronosis appears.[8-10]

HGA is a strong reducing substance that produces a positive reaction with Benedict's and Fehling's reagent. With Fehling's ($FeCl_3$) reagent, it gives transient blue-green Color.[11,12] The diagnosis of alkaptonuria is made by demonstrating homogentisicaciduria and is confirmed by measurement of HGA concentration in the urine by paper and thin layer chromatography[13] and photometry.[11] HGA is not elevated in the blood but excreted in the urine in heavy amounts - as much as 4-8gm / day.[14]

Clinical aspects: Alkaptonurics are asypmtomatic in childhood as homogentisicaciduria is the only manifestation in this age group.[8,15] Staining of the diapers may indicate the disease in infancy.[15] Ochronosis does not occur in tissues until there is long exposure to HGA. Patients with alkaptonuria are usually not aware of the disease until about the age forty when symptoms become evident.[9,10] Pigmentation of the sclera or earlobe starts appearing with the advancing age.[10,16]

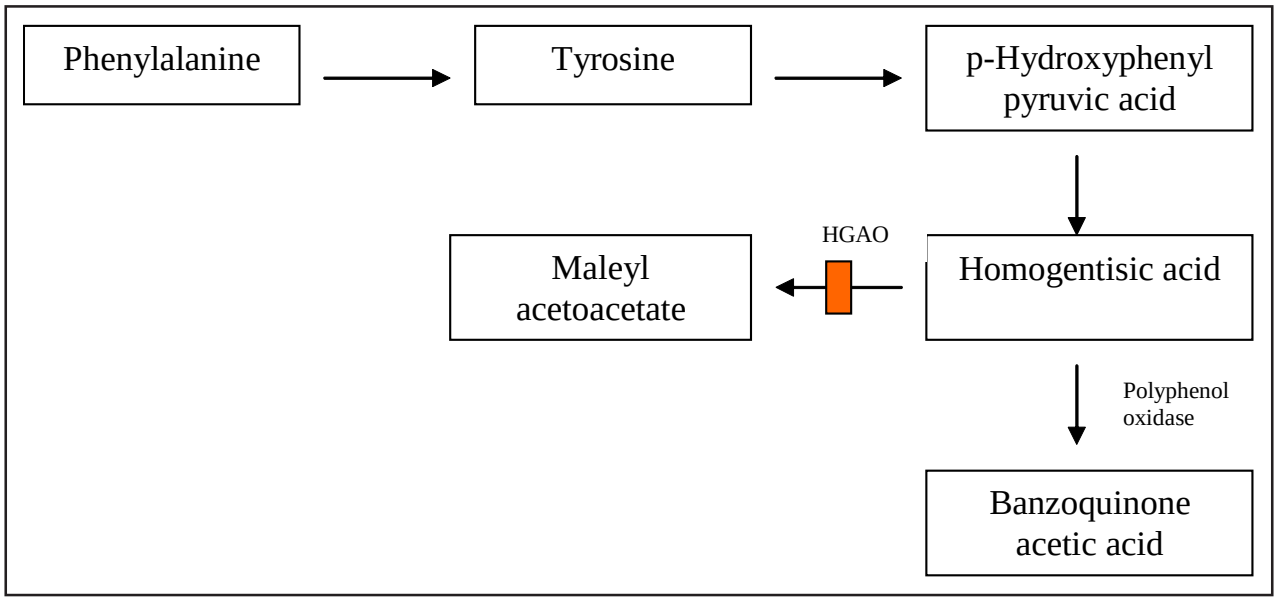

Figure-1: Showing metabolic pathway of phenylalanine, tyrosine and HGA and the site of metabolic block responsible for AKU.

Skin takes blue-black speckled discoloration.[16,17] Teeth and nails may also show ochronotic discoloration.[17]

Arthropathy is common,[8,9,18,19] deposits of pigment cause cartilage to become brittle and eventually to break apart (fragment). This occurs almost in all patients in the third or fourth decade of their life.[9] The earliest symptom appears in the knee, hip, shoulder or lumbar spine, resembling rheumatoid arthritis or osteo-arthritis,[8,9] often necessitating joint replacement.[8,18,19] The degenerative changes in the lumbar spine are quite characteristic with narrowing of joint spaces and fusion of vertebral bodies resulting in marked limitation of movements with complete ankylosis.[9] The disease is more severe in males whereas the incidence is the same in both sexes.[8,9]

There is a high incidence of heart disease. The aortic and mitral heart valves are most affected.[18,20,21] Ochronotic granules can cause valves to calcify or harden. Pigment deposits can lead to the formation of atherosclerotic plaques containing cholesterol and fat.[20] Secondary calcification of the aortic valve may necessitate aortic valve replacement.[18] Ischaemic heart disease with ultimate myocardial infarction is the leading cause of death. Heavy pigment deposits in the cartilage of the larynx, trachea and the bronchi are common.[22] Renal calculi also develop due to deposition of pigment in the kidneys.[8,19] In man, pigment deposits can form stones in the prostate.[8]

Genetics: Genetically AKU is transmitted as an autosomal recessive trait.[1,4,5] Garrod's suggestion that the disorder results from absence in the liver of the enzyme that catalyzes the oxidation of HGA, gave rise to the one gene - one enzyme hypothesis, leading to the notion of inborn errors of metabolism and the field of biochemical genetics. It has been demonstrated that mutations of the alkaptonuria gene, located on chromosome $3q^{21}$- q^{23} in human, leads to the production of an inactive HGAO protein.[23] Pollak et al[24] used homozygosity mapping to locate the alkaptonuric gene to $3q^2$ in a 16–cM region. In 1996, Fernandez-Canon et al[25] cloned the gene for homogentisate 1,2 dioxygenase (HGD, EC 1.13.11.5), and they demonstrated that HGD harbors the mutation that co-segregates with the disease and provided biochemical evidence that at least one of these missense mutations is a loss of function mutation.

Treatment: Currently no effective cure is available. High doses of ascorbic acid may prevent deposition of the polymerized ochronotic pigment and may therefore prevent or delay subsequent symptoms.[15,26,27] Low protein diet especially low in phenylalanine and tyrosine is advocated in combination with ascorbic acid.[27] A new medicine _ Nitisinone that inhibits the enzyme, which produces HGA is on trial for the evaluation of long-term therapy.[8]

CONCLUSIONS

This study indicates that AKU also occurs in Pakistan. Usually there is history of consanguineous marriage in the parents of affected siblings. However, the parents of the reported cases here were unrelated to each other before marriage but hailed from the same tribe/cast. The present study also suggests the recessive type of inheritance already established in this condition although there is no consanguinity. Early detection is important for prevention and treatment of multiple systems. The detection of this disorder is not without benefit for the affected individual as the administration of un-necessary drugs can be avoided.

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