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A review on alkaptonuria

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ABSTRACT

An unusual condition with autosomal recessive inheritance is Alkaptonuria (AKU). It is caused by a mutation in a gene that results in homogentisic acid accumulation (HGA). Characteristically, excess HGA means that sufferers move through dark urine, which turns black while standing. This is a trait that is present from birth. Over time, patients experience other AKU symptoms due to collagenous tissue deposition of HGA, including ochronosis and ochronotic osteoarthropathy. While this disease does not decrease life expectancy, the quality of life is greatly affected by it. Despite gaps in understanding, the natural history of this disease is becoming better known. Along with the introduction of a potentially diseasemodifying treatment, clinical evaluation of the disorder has also increased. In addition, recent advances in AKU science have contributed to a new understanding of the condition and further research of AKU arthropathy have the ability to affect osteoarthritis management therapy.

Keywords: Alkaptonuria, Osteoarthritis, Homogentisic acid, Ochronosis, Ochronoticarthropathy, Homogentisate 1, 2 Dioxygenase.

INTRODUCTION

Alkaptonuria is a rare hereditary condition that occurs due to homogentisic acid oxidase deficiency, resulting in dark-colour urine, ochronosis, and ochronoticarthropathy triads. Normally, life expectancy is normal. The frequency of alkaptonuria is 1 in 250000 to 1 in 1000000 live births. India has reported only a few cases [2]. Alkaptonuria is caused by a mutation on your homogentisate 1,2-dioxygenase (HGD) gene. It's an autosomal recessive condition.This means that both of your parents must have the gene in order to pass the condition on to you.Alkaptonuria is a rare disease. The alkaptonuria affected patients list worldwide [Figure 1] [4].

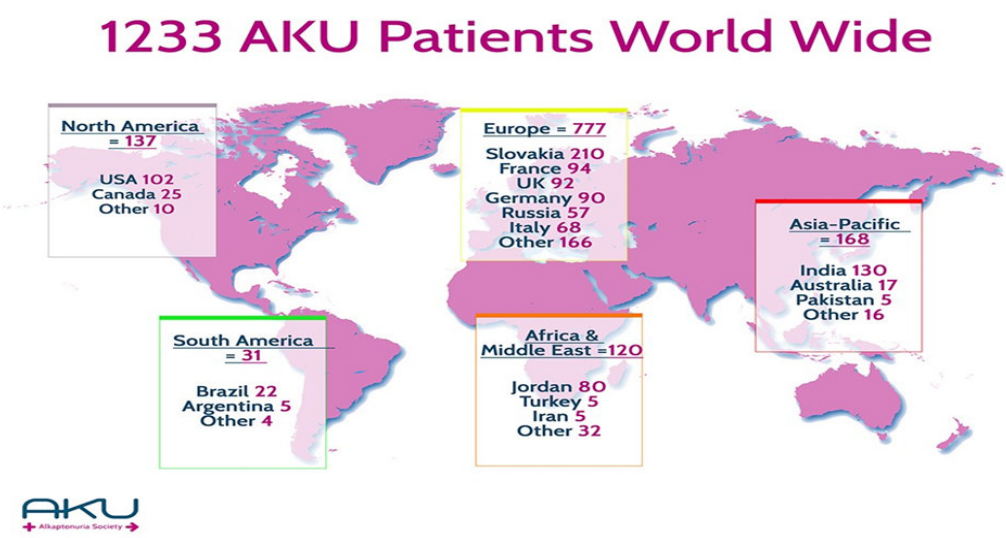

Figure 1Overview of the number of patients with alkaptonuria reportedworldwide [3]

HISTORY

In 1908, Garrod's use of AKU in the Crown lectures brought the situation into thespotlight. Documentation of the disease started in the 16th and 17th centuries.24 The earliest clinical case of AKU was identified in the Egyptian mummy Harwa, which is thought to date back as far as 1500 BC.33 The term Alkaptonuria is derived from the Arabic word "alkali" (meaning alkali) and the Greek word meaning "alkali" (meaning alkali) and the Greek word meaning "alkali" (meaning alkali).In 1866, Ochronosis was first described and named by Virchow, because the HGA pigment appeared to be ochre (yellow/brown) in colour under microscopy.34 In 1891, HGA was identified as the causative component and named a benzoic acid derivative because of its close structural association with gentisicacid.1,21,35,36 In 1995, the genetic defect was discovered, cloned and mapped to chromosome .[11]

SYMPTOMS

One of the early symptoms of Alkaptonuria is dark stains on a baby's diaper. Other signs during childhood are few. As you age, signs become more apparent. When exposed to the air, your urine can turn dark brown or black. [Figure 2]You might see signs of early onset osteoarthritis by the time you hit your 20s or 30s.For example, in your lower back or broad joints, you might experience chronic stiffness or discomfort. There are other signs of alkaptonuria:[4]In the sclera (white) of your eyes, dark spots. In your face, the thickened and darkened cartilageSpeckled blue discoloration of the skin, particularly around the sweat glands.Darkcolored stains of oil or sweat With black earwaxProstate stones and kidney stones Via arthritis (especially hip and knee joints)Alkaptonuria may contribute to heart attacks as well. Homogentisic acid accumulation induces hardening of the heart valves. This may prevent them from completely shutting, leading to aortic and mitral valve disorders [3].

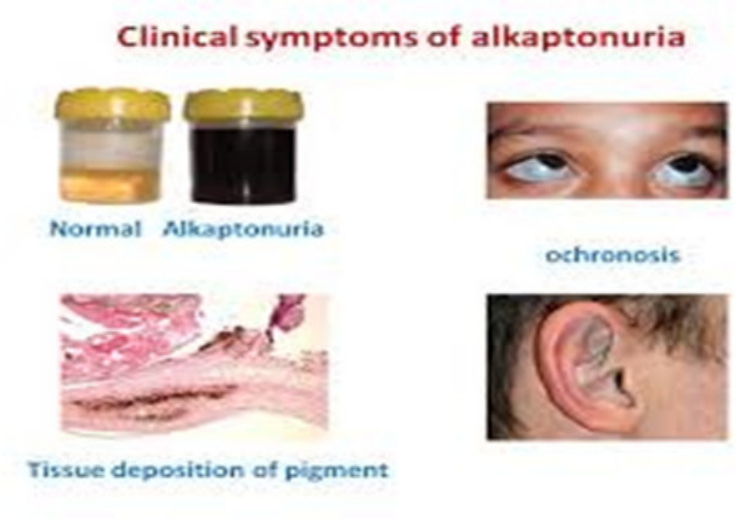

Figure 2 Symptoms of alkaptonuria

DIAGNOSIS

When characteristic symptoms, a clear medical history, a comprehensive clinical examination and a number of advanced tests are established, the diagnosis of alkaptonuria is made. It is characteristic of alkaptonuria to identify vastly high levels of homogentisic acid in the urine. In persons with dark urine, Alkaptonuria should be suspected. However, because some individuals with alkaptonuria may not have dark urine, it might be advisable for all people with osteoarthritis, especially those with early onset of symptoms, to rule out the condition. Urine of a 4-month-old baby with dark urine (on the left) after 10% ammonia and 3% silver nitrate were added. The tube in the middle is a normal control. Color change on alkalization is not a specific test, and confirmatory investigations are needed**.** [Figure 3][5].

Figure 3 Sample of urine

WORK-UP AND CLINICAL TRIALS

A gas chromatographymass spectrometry analysis can detect elevated levels of homogentisic acid in the urine. To assess the nature and degree of joint and spinal disease or the involvement of the aortic or mitral valves, different imaging techniques may be used.On a clinical basis, molecular genetic testing that can identify mutations in the HGD gene is available.

To confirm the diagnosis, however, this testing is not neededWaves (echoes) bounce off the heart, allowing doctors to research cardiac function and motion.For detecting coronary artery calcification, computed tomography (CT) scanning may be recommended [8].

PATHOPHYSIOLOGY

Chemical skeletal formula of homogentisic acid, which accumulates in the body fluids of people with alkaptonuria[10][Figure 4].

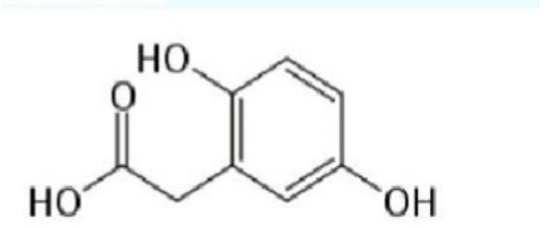

Figure 4 Chemical structure of alkaptonuria

All individuals bear two copies (one obtained from each parent) of the HGD gene in their DNA, which incorporates genetic information to create the 1,2dioxygenase (HGD) enzyme homogentisate that can normally be found in various tissues in the body (liver, kidney, small intestine, colon, and prostate)Both copies of the gene contain defects in people with alkaptonuria, meaning that the body does not generate an enzyme that works properly.HGD mutations are normally found in some sections (exons 6, 8, 10, and 13), but the gene has identified a total ofover 100 abnormalities.[4]The normal HGD enzyme is a hexamer (it has six subunits) organised into two classes.The structure, function, or solubility of the enzyme may be affected by different mutations.[4] Quite rarely, the disease tends to be transmitted in an autosomal dominant way, where alkaptonuria is associated with a single defective copy of HGD from a single parent;[8]other mechanisms or defects in other genes may be responsible in such cases It is due to the absence of functional homogentisatedioxygenase (HGD) in the liver. [9][Figure 5].

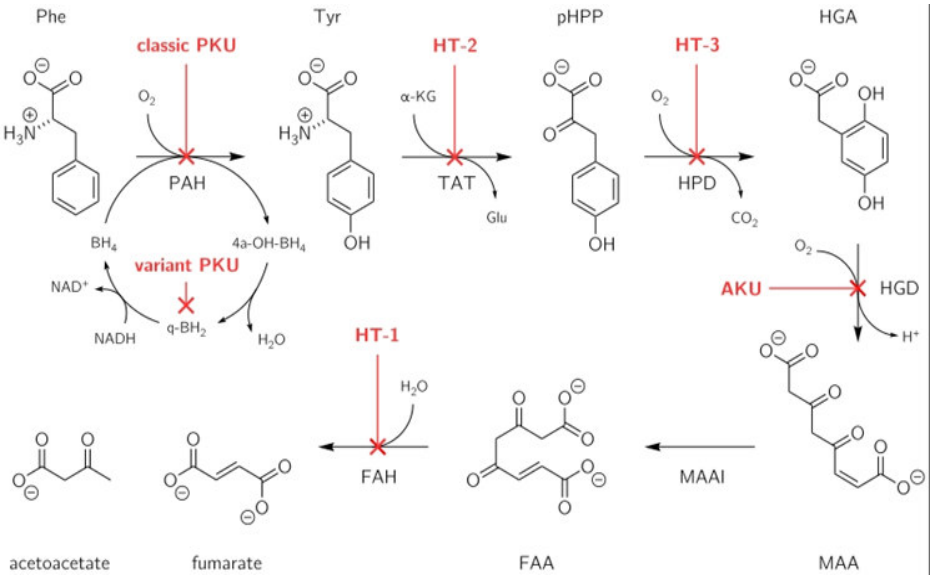

Figure 5 Pathophysiology of alkaptonuria

TREATMENT

Alkaptonuria is a chronic disease and there is no clear therapy or cure at present.A medication called nitisinone, however, has shown some promise, and painkillers and changes in lifestyle can help you cope with the symptoms.Nitisinone is not approved for alkaptonuria and is available "off label" at the National Alkaptonuria Clinic, a treatment center for alkaptonuri [6]. Nitisinone decreases the amount in the body of homogentisic acid.The AKU Society has details on the clinical trial program for nitisinone, DevelopAKUre. The Diet if the disease is diagnosed in infancy, by limiting protein in the diet, it may be possible todelay its development, as this may decrease the levels of tyrosine and phenylalanine in the body.Allowprotein diet can also be useful in minimizing the risk during adulthood of the possible side effects of nitisinone. You can be informed about this by your doctor or dietitian.Practice you might think exercising would make the symptoms worse if alkaptonuria causes pain and stiffness. But daily gentle exercise can actually help with muscle building and joint strengthening. [7] The drug is currently in phase[III],meaning that the drug is given to a large group of people and its metabolic process can be shown in [Figure 6].

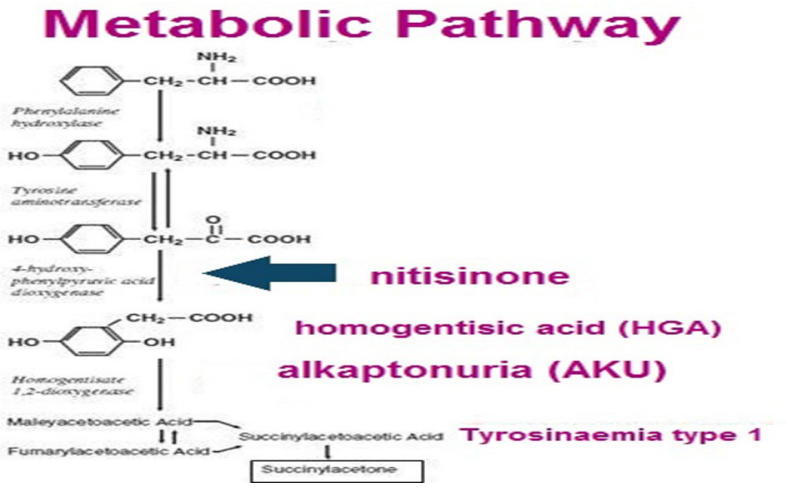

Figure 6Metabolic pathway of alkaptonuria

EXERCISE

It is also beneficial for stress control, weight loss and posture enhancement, all ofwhich will relieve the symptoms.The AKU Society recommends avoiding exercise that places extra pressure on the joints, such as boxing, football rugby, and instead attempting gentle exercise such as yoga, swimming, and Pilates.You should help your GP or a physiotherapist come up with an acceptable workout schedule to follow at home. Following this plan is important because there is a risk that the wrong form of exercise may damage your joints.

PAIN RELIEF

Please speak to your doctor about painkillers and other pain relief strategies. Learn about pain living, emotional assistance .At first, it can be frustrating and daunting to diagnose alkaptonuria. Many who learn they have alkaptonuria, like many people with a longterm health condition, may feel nervous or depressed.But there are individuals with whom you can interact that can help. If you find you need help to deal with your disease, talk to your GP. You can access theAKU Society website as well.Anorganization providing patients, their families and caregivers assistance [7].

SURGERY

Procedure often, if joints are weakened and need to be replaced, or if heart valves orvessels have hardened, surgery may be required.Learn about some procedures that are common: Replacement hips, Replacement of the Knee, Replacement of the Aortic Valve[6].

SURVEILLANCE

Echocardiography for detecting aortic dilation, aortic or mitral valve calcification, and stenosis in

persons older than 40 years; CT for detecting coronary artery calcification.[7]Agents/circumstances to avoid: In order to try to minimize the development of extreme arthritis, physical stress on the spine and large joints, like hard manual labour or high-impact sports.

GENETIC COUNSELING

In an autosomal recessive manner, Alkaptonuria is inherited. Each sib of an infected person at conception has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. If all HGD pathogenic variants in the family are identified, carrier testing for at-risk relatives and prenatal testing for a pregnancy at elevated risk are possible. [7]

CONCLUSION

Alkaptonuria must be considered in the evaluation of low back pain of patients especially with having a positive family history and bluish discoloration of cartilage tissues.

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