Prevalence of Alkaptonuria among group of patients with low back pain in Erbil

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Abstract:.

ALKAPTONURIA (AKU) It is an autosomal recessive disorder due to deficiency of homogentisic acid oxidase, The homogentisic acid retained in the body is deposited as a pigmented polymer in the cartilage, skin and sclera in addition passing dark urine or when fresh urine turns black on standing or on alkalization. The darkening of the tissues by this pigment is designated Ochronosis

This is across sectional study carried on 7500 patients presented with low back pain in Rzgary General Teaching Hospital and private clinic in the period from May 2005-march 2010 (57 months) ,in Erbil Governorate ,Iraq.

The study was conducted to record information regarding the gender, age, race, incidence, frequency of joint involvement.

Complete history were taken from all patients of passing dark urine or when fresh urine turns black on standing or on alkalization ,and finding of characteristic radiographic changes to the spine

The lumber spine and hip joint were the most frequently affected joints in the study group while sacroiliac joint and peripheral joints were spared

CONCLUSIONS:

This study indicates that AKU also present in Erbil-Iraq .a question for urine colure changes is advise when taking history from patients with low back pain specially when diagnosing patients with ankylosing spondylitis. Early detection is important for prevention and treatment of multisystem. As the administration of unnecessary drugs can be avoided

Keywords: alkaptonuria, ochronosis, arthritis, dark urine

Introduction

ALKAPTONURIA (AKU) is a rare inherited genetic disorder of tyrosine metabolism. It is an autosomal recessive disorder due to deficiency of homogentisic acid oxidase (HGO), an important enzyme in the catabolism of aromatic amino acids. It catalyzes the conversion of homogentisic acid to maleylacetoacetic, which is ultimately converted to fumaric and acetoacetic acid [1] .The homogentisic acid retained in the body is deposited as a pigmented polymer in the cartilage and, to a lesser degree, in skin and sclera. [2].It is of interest to note that the disease was identified in 1500 BC in an ancient Egyptian mummy. [3]

The condition is rare, affecting one in 250,000 to one million people worldwide, in US; the incidence is 1 case per 4 million populations. [4] Cases have also been reported from UK, Germany, Lebanon, Sudan, Saudi Arabia, Turkey and other parts of the world.[5,6] .Alkaptonuria affects males and females in equal numbers, although symptoms tend to be more severe in males and most severe in those individuals with impaired kidney function.[4]

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. The widespread deposition of pigment in alkaptonuric patients is called ochronosis,[7,8]a term used to describe the darkening of tissues, which is due to a slow accumulation of the black polymer of homogentisic acid in the cartilage and other mesenchymal tissues and arthritis of weight bearing joints.[9]

The diagnosis is conformed by a history of passing dark urine or when fresh urine turns black on standing or on alkalization with the onset of arthritis .Dark pigmented synovium may by seen on arthroscopy. A specific enzymatic method permits quantization of homogentisic acid in urine and blood and molecular cloning of the homogentisic acid oxidase HGO gene makes detection of heterozygotic carriers possible [10] .Also the diagnosis is made by measurement of homogentisic acid in the urine where it turns black upon exposure to oxygen or alkali treatment, and characteristic radiographic changes to the spine.

Treatment

Individuals with alkaptonuria are counseled to avoid occupations in which the large joints and spine are subjected to stress. There have been attempts to prevent symptoms by consuming a low protein diet especially low in phenylalanine and tyrosines are advocated in combination with ascorbic acid. [11]. these regimens have had no effect on the disorder. Other treatment is symptomatic and supportive. Anti-inflammatory medication may be of benefit in reducing pain. Joint and valve replacement may provide symptomatic relief.

A new drug (Nitisinone) that inhibits the enzyme, is on trial for the evaluation of long-term therapy. [12, 13]

Objective of the study are:

1-Measuring the prevalence of AK in the studied sample.

2-Discribe the clinical features and presenting symptoms of patient with AK.

Patients & Method

This is a cross sectional study carried on 7500 patients presented with low back pain in Rizgary General Teaching Hospital and private clinic in the period from May 2005-March 2010 (57 months), in Erbil Governorate ,Iraq.

Ochronosis was diagnosed on the basis of compatible clinical picture such as a history of passing dark urine or when fresh urine turns black on standing or on alkalization [4] (which were found in all studied patients) ,and characteristic radiographic changes to the spine .

Complete history was taken from all patients, asking for any complaint of gradually increasing pain and stiffness in the lower back.

Any patients with history of trauma, fever, oral ulcers, conjunctivitis, acute abdominal pain, and dysuria or recurrent diarrhea are excluded from this study.

All the patients were examined fully for any skin discoloration, restriction of chest expansion at respiration, tenderness over the spine, marked limitation of movements of the spine (positive schober test), decrease range of movements of the large joints and the presence of cripitus.

Complete blood count (CBC) and film, erythrocyte sedimentation rat (ESR), C-reactive protein (CRP), latex fixation test and anti nuclear antibody (ANA) are done for all patients with positive history of passing dark urine or when fresh urine turns black on standing or on alkalization.

X-rays of the spine for calcification of intervertebral discs; sacroiliac joints to exclude abnormalities, and looking for any osteoarthritic radiological feature at uncommon sites for osteoarthritis. Ultrasounds of abdomen, echo study of the heart were also done.

Results

Out of 7500 patients with low back pain only six patients met the criteria for the diagnosis of ochronosis., all of whom were males.

Prevalence of AK among studied sample was: 8/10 000

Figure 1; show the age distributions of the patients. five are male and one was female gender.

Two patients from the rural area while; four are from urban area.

Four patients are Kurdish, one Turkish & one Arab according to race distribution Table (1).

Table (2) shows the distribution and frequency of different symptoms and sign, all patients had a history of

voided normal urine changed to dark colour after a variable period of air exposure.

Hip joint was the most frequently affected joints in the study group 50 % of patients, followed by shoulder joints 33,3 % (Table 3).

Table (4) shows investigations done for the studied patients including urine after adding FeCl3.

X-rays shows that all cases had calcified narrowed intervertebral disk & all patients had normal sacroiliac joints, Table (5).

Discussion

Ochronosis is a rare condition. There are no clear data about the incidence of the disease in Iraq, so this number may reflect the incidence of the disease in Erbil noting that one of the patients was Turkish who works in Erbil. [16].

Alkapton uric patients are usually asymptomatic as children or young adults.[12 ,13] When they get older, pigmentation of the sclera or the cartilage of the ear start to appear(as showed in figure 2) ,[7] or it may involve the skin, giving these areas a dusty coloration (figure 3) . Strong 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; in this study the urine of all four cases has spontaneous change in the color after variable period, maximum 12 hours after air exposure and all the cases are middle-aged and elderly. [14, 15] (Figure 4.)

Although it has been reported that the male to female incidence are equal, and the disease is more severe in men, this study showed that all the cases in this study were males, and this may be due to the fact that the male carries a more severe form of the disease and the mild form in female may be passed undiagnosed. [4,12]

Arthritis is one of the disabling effect of this condition, and occurs in almost all patients with advancing age [17] .The earliest symptoms are usually in the spine, hips and knees, (large peripheral joints and more in weight-bearing),while the peripheral small joints are usually spared ,which founded in all the cases. The radiological picture is of severe osteoarthritis. In contrast to osteoarthritis, the large joints like hip and shoulder are most commonly involved; where as the sacroiliac joints are usually spared (Figure 6). The degenerative changes in the lumbar spine are quite characteristic, with narrowing of disk spaces, calcification and fusion of vertebral bodies, (Figure 5), resulting in marked Limitation of motion with ultimate ankylosis. In current study all six cases had these spine changes. Ochronotic Arthropathy in the hips and the knees may be so severe as to require total joint arthroplasty [18]; one of six cases had positive family history of joint replacement. .There is a high incidence of heart disease [19], commonly due to mitral and aortic valvulitis which not founded in this

study. Secondary calcification of the aortic valve may be so severe as to necessitate urgent aortic valve replacement [20].

Figure (7& 8) shows the improvements of the discoloration in one of the patients after 30 months of receiving 500-1000 mg of vitamin C.

CONCLUSIONS

This study indicates that AKU also occurs in Erbil- Iraq, a question for urine colure changes is advise when taking history from patients with low back pain specially when diagnosing patients with ankylosing spondylitis. Early detection is important for prevention and treatment of systemic complications mainly joints, spine and vital organs, and the avoidance of the administration of unnecessary drugs.

References

1- La Du BN. Alcaptonuria. In: Stanbury JB, Wyngaarden JB, Frederickson DS, editors. The metabolic basis of inherited disease. 4th edition. New York: McGraw-Hill 1978:268-82.

2- Gaines JJ Jr, Tom GD, Khankhanian N. The ultra structural and light microscopic study of the synovium in ochronotic arthropathy. Hum Pathol 1987; 18:1160-1164.

3- Stenn FF, Milgram JW, Lee SL, Weigand RJ, Veis A. Biochemical identification of homogentisic acid pigment in an ochronotic egyptian mummy. Science 1977; 19 7:566-8

4- La Du BN. Alkaptonuria in the Metabolic & Molecular Basis of Inherited Diseases. (8th edition), Scriver CR, Beandet AL, Sly WS, Valle D,(Eds), New York, McGraw Hill 2001;2109-23.

5- M Al-EssaL, Al – Shamshan MS, Rasheed PT. Ozaond, Alkaptonuria. Case report & review of the Literature. Ann Saudi Med 1998; 18(5):442-4.

6- Fakatselli NM, Hudaverdi EY. Alcaptonuria. Pak Paed J 1973; III: 19-22

7- Sickert RG, Gibilisco JA. Discoloration of the teeth in alkaptonuria (ochronosis) and Parkinsonism. Oral Surg Oral Med Oral Pathol 1970; 29:197-9.

8- Fisher AA, Davis MW. Pigmented sclera: A diagnostic challenge. Postgrad Med J 2004; 80:493-4

9- Milch RA. Studies of alkaptonuria: inheritance of 47 cases in eight highly inter-related Dominican kindreds. Am J Hum Genet 1960; 12:76-85.

10-Fernandez-Canon JM, Grandadino B, Beltram-valero de Bernabe D,et al. The molecular basis of alkaptonuria Nat Gemet 1996; 14: 19-24.

11- Morava E, Kosztolanyeg, Engeke U. Reversal of Clinical symptoms and radiographic abnormalities with protein restriction and ascorbic acid in alkaptonuria. Ann Biochem 2003; 40:108-10.

12- Phornphutkul C, Introne WJ, Perry MB. Natural history of alkaptonuria. New Engl J Med 2002, 347; 26:2111-21.

13- Suwannarat P, O'Brien K, Perry MB, et al. Use of nitisinone in patients with alkaptonuria. Metabolism. 2005; 54:719-28.

14- La Du BN Jr: Alkaptonuria and ochronotic arthritis Mol Biol Med 1991; 8:31-8.

15-Turiansky GW, Levin SW. Bluish patches on the ears and axillae with dark urine: ochronosis and alkaptonuria; Int J Dermatol 2001; 40:333-5

16- Khalid A.O. AL-Dabbagh, Alkaptonuria, a rare inherited disorder: a case report and review of literature.Tikrit Medical Journal 2008; 14 (2): 135-137.

17- O'Brien WM, Banfield WG, Sokoloff L. Studies on the pathogenesis of ochronotic arthropathy. Arthritis Rheum 1961; 4:137-8.

18- Carrier DA, Harris CM. Bilateral hip and bilateral knees arthroplasties in a patient with ochronotic arthropathy. Orthop Rev 1990; 19:1005-9.

19- Vavuraankin M, Triantafillidn H, Stefonadin C. Aortic stenosis & Coronary artery disease caused by alkoptonuria; A rare genetic metabolic syndrome; Cardiology 1998;90(4):302-4.

20-Dereymaeker L, Van Parijs G, Bayart M, et al. Ochronosis and alkaptonuria: report of a new case with calcified aortic valve stenosis. Acta Cardiol 1990; 45:87-92.

Table 1. Race distribution.

Signe & Symptoms	No.	%
Back stiffness	6	100%
Back pain	6	100%
Buttock ache	0	0
Skin discoloration	2	50%
Discoloration of sclera	2	33.3 %
Change in color of urine	6	100%
Family history	1	16,6 %
Schober test +ve	6	100%

Table (2) Distribution and frequency of clinical features

Joint	No.	%
Knee joint	1	16,6 %
Hip joint	3	50 %
Shoulder joint	2	33.3 %
Ankle joint	0	0
Wrist joint	0	0
elbow	1	16.6 %
Dorsal spine	4	66.4 %
Lumbar spine	6	100%
Cervical spine	1	16.6 %
Sacroiliac unilateral	0	0
Sacroiliac Bilateral	0	0

Table 3 Frequency of joint & spine involvement

Variable	normal	Abn.
ESR	6	0
WBC(/mm3); 4000-11000	6	0
Urine exam by screen test	0	6
C-reactive protein	6	0
Ultra sound of abdomen	6	
Variable	+ve	-ve
Latex fixation test	1	5
ANA	0	6
Echo study (valve calcification)	1	5

Table 4 shows laboratory finding

Abnormalities	No.	%
No abnormalities	0	
Decrease disc space	6	100%
Erosion	0	0
Calcified disk	6	100%

Table 5. The radiological finding in the spine

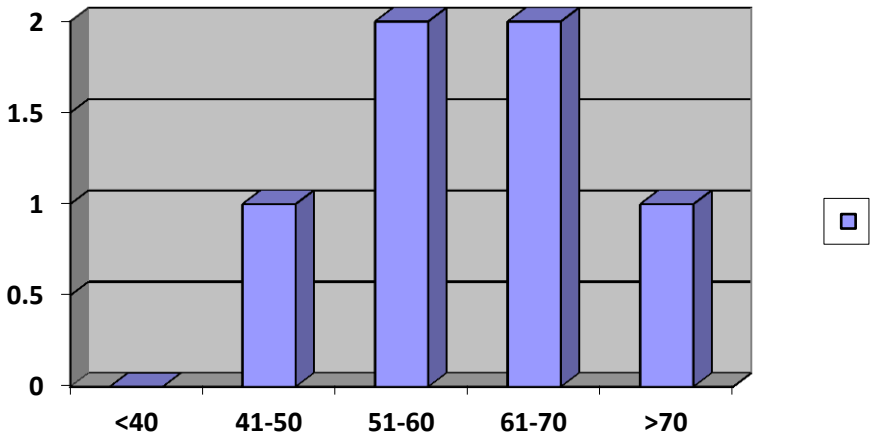

Figure 1 shows age of the studied groups

Race	No.	
Kurdish	4	
Arabic	1	
Turkish	1	
Total	6	

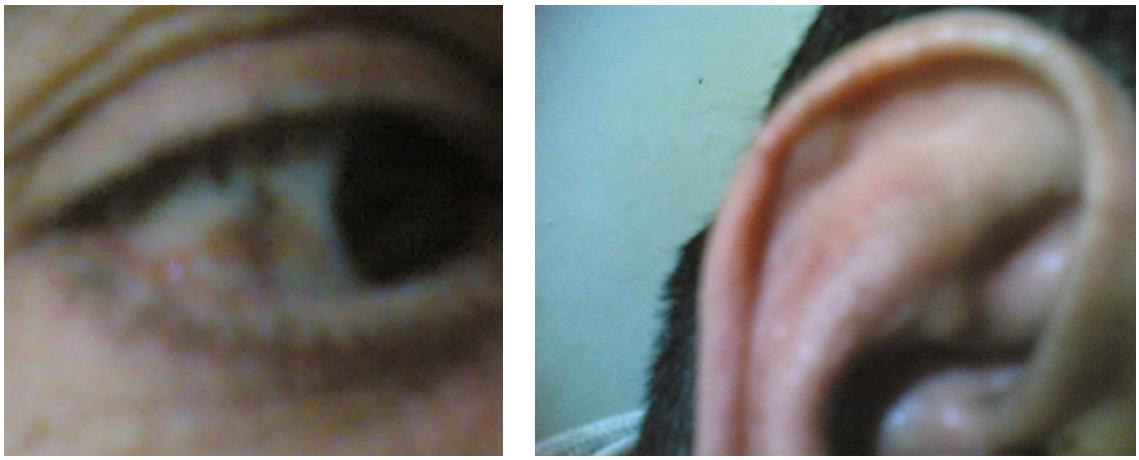

Figure 2. Ear &sclera discoloration.

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Figure 3, skin discoloration at both cheeks and indices.

Fig 4, Urine after 1st hour after 12 hour

Figure 5, X-rays showed sever OA changes at both shoulders joint.

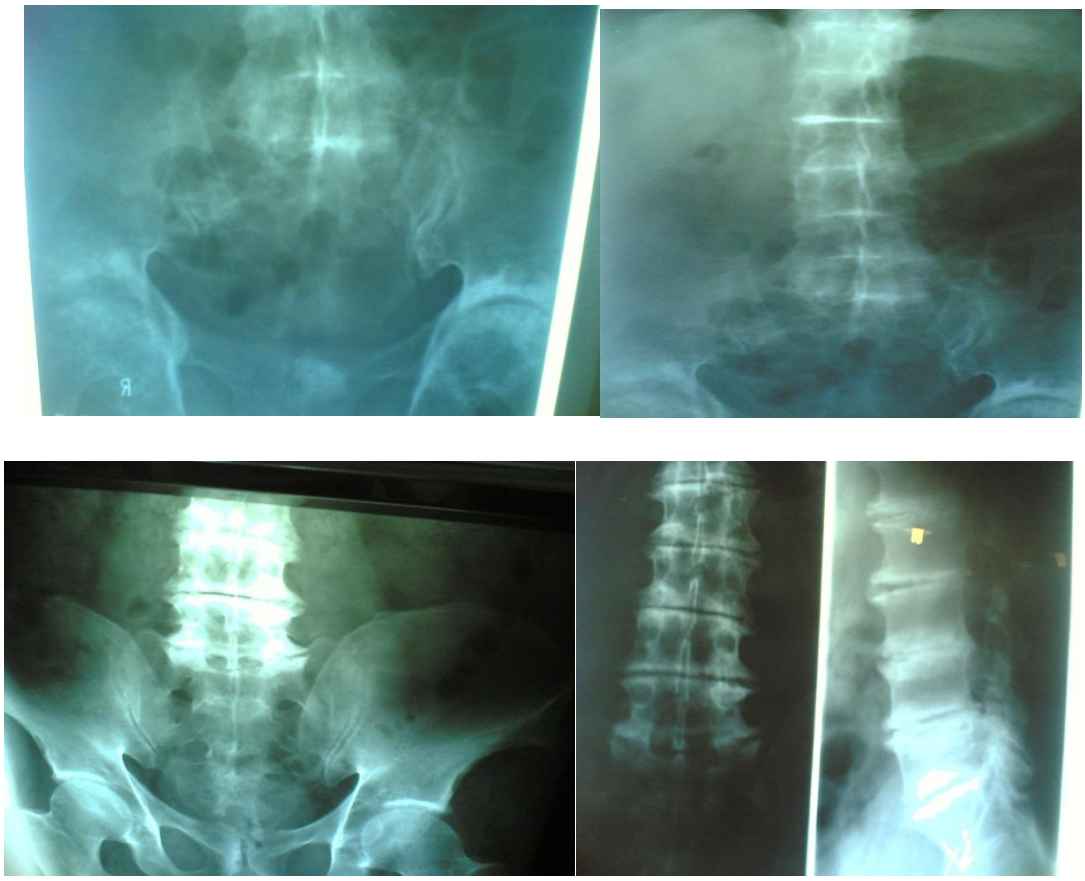

Figure 6, X-rays of patients showed normal SI joint, calcified disks, OA hips

Figure 7, shows change of color of the indices of the same patient above after treatment

Figure 8 shows the improvement in the color of face after treatment

skin discoloration at both sclera and indices in another patient