

Case Report Article

Misdiagnosis of alkaptonuria in an elderly patient

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Abstract

Alkaptonuria is a rare hereditary metabolic disorder, resulting from deficiency of enzyme homogentisate 1,2-dioxygenase (HGD). Its features include spine and peripheral joint arthritis, as well as bluish discoloration of cartilage tissues. We report a case of an 81 year old male with a 5 year history of low back pain and progressively increasing stiffness of the spine, incorrectly diagnosed as ankylosing spondylitis and treated with non steroid anti-inflammatory drugs (NSAIDs) and sulfasalazine. Diagnosis of alkaptonuria was based on the characteristic ochronotic pigmentation of ears and eyes cartilage and typical radiographic findings of the spine-narrowed intervertebral spaces and intervertebral disc calcification, combined with the presence of homogentisic acid in the patient's urine. Complete history, physical and radiological examinations revealed severe degenerative arthropathy of knee, hip and shoulder joints, which had led to bilateral total hip and knee arthroplasty in the last 7 years. Due to the patient's cardiovascular comorbidity and advanced age, surgical treatment of ochronotic spine arthropathy was not considered. Management of the patient was based on analgesic treatment and vitamin C. Although alkaptonuria is a rare disease it should be considered in patients, even the elderly ones, who present with low back pain and severe degenerative arthropathy.

Keywords: Alkaptonuria, Ochronosis, Homogentisic acid (HGA), Low back pain, Degenerative arthropathy

Introduction

Alkaptonuria (AKU) is a very rare inherited recessive autosomal metabolic disorder with an estimated prevalence ranging from 1:200.000 to 1:1000000 live births worldwide^{1,2}; it is caused by homogentisate 1,2-dioxygenase (HGD) deficiency, an enzyme responsible for converting homogentisic acid (HGA) to maleylacetoacetic acid in the tyrosine degradation pathway^{1,2}. The gene encoding HGD has been mapped to human chromosome 3q 21-q23³⁻⁵. To date, more than 90 mutations of the HGD gene have been described, reflecting the disorder's clinical variability².

The inability to metabolise tyrosine and phenylalanine leads to HGA accumulation in the blood; the amount excreted in the urine turns dark brown or black on oxygenation or alkalization^{6,7}. This typical urine colour occurs early in the disease course but may not be noticed; fresh urine often seem normal and it may take several hours after voiding for the colour changes to occur. Homogentisic acid products resemble melanin and are deposited in the collagen, particularly the cartilage; the resulting tissue colour (ochre) gives the name ochronosis to the process⁸.

The three major features of alkaptonuria are the presence of HGA in the urine, ochronosis (connective tissue bluish-black pigmentation) and spondylarthropathy involving the axial and appendicular skeleton (arthritis of the spine and larger joints). Both synovial and intervertebral joints are affected⁹. Usually, joint symptoms start between the ages of 40 and 50 years. There is a predominance of men relative to women 2:1¹⁰. Less common manifestations include renal, urethral, and prostatic calculi, cardiovascular abnormalities and valvular disease^{7,11,12}.

There is no validated assay of HGA in blood. The diagnosis

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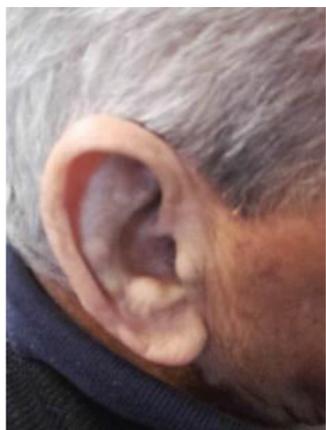


Figure 1. Black -bluish discoloration of the ear.



Figure 2. Sclera pigmentation.



Figure 3. X-ray of the thoracic spine of the patient.

of alkaptonuria is based on the detection of a significant amount of HGA in the urine by gas chromatography - mass spectrometry analysis. The amount of HGA excreted per day in patients with alkaptonuria is usually between one and eight grams. Identification of biallelic HGD pathogenic variants on molecular genetic testing confirms the diagnosis and allows family studies⁶.

Treatment of this metabolic disorder is generally supportive and aimed at preventing or minimizing the effects of ochronotic arthropathy. Knee, hip and shoulder replacement should be a therapeutic option when needed as well as the surgical intervention for prostate and renal stones. Aortic stenosis may necessitate valve replacement too⁶.

Case report

An 81 year old man, with a 5 year history of progressive low back pain and increasing stiffness of the spine, referred to our outpatient clinic. He also mentioned two similar but short-term incidents in his past medical history, starting at the age of 60. From his past medical history, total replacement of both knees and hips in the course of the last 7 years was noted; it was attributed to degenerative arthropathy. He had been diagnosed with Ankylosing Spondylitis and was treated with NSAIDs and Sulfasalazine for the last 5 years without noteworthy amelioration. He was also treated for atrial fibrillation and arterial hypertension.

On initial physical examination, his vital signs were normal. During the head and neck examination a bluish/black discoloration of the external ears was found and two angular sclera pigmentations were noticed (Figures 1, 2). On spine examination, no tenderness was found but a severe spine motion limitation was prevalent. The Schober's test was positive and positive Straight leg test was detected bilaterally. The patient mentioned morning stiffness of less than 10 minutes and his back pain exhibited mechanical rather than inflammatory qualities. He also reported bilateral lower limb pain, with right side dominance. Peripheral joints examination was normal except for the shoulders, where limitation of motion was found in all movement axes.

The blood test results including C-reactive protein, rheumatoid factor and HLA -B27 were negative. Results of all other routine studies were within normal limits. Radiological examination (Plain radiograph and Computing Tomography-CTscan) of the thoracic and lumbar spine revealed narrowing of intervertebral disc spaces and prominent wafer-like disc calcification, together with osteophyte formation and calcification of the intervertebral ligaments. Lumbar CT scan showed an orbital narrowing of L5-S1 intervertebral disc with right L5 nerve root pressure, a finding compatible with his lower limbs symptoms (Figures 3, 4). An additional lumbar spine CT scan finding was sacroiliac joint calcinosis (Figure 5).

The diagnosis of ankylosing spondylitis was considered on the basis of spinal involvement with anterior ligament calcification and sacroiliitis and large peripheral joints



Figure 4. Lumbar and thoracic spine CTscan.



Figure 5. Sacroiliac joints CTscan. Radiographs of shoulders showed joint space narrowing, subchondral cysts and osteophyte formation.



Figure 6. X-rays of the right and left shoulder of the patient.

involvement (namely hips, knees and shoulders), but the lack of response to treatment together with the presence of extended calcification of all intervertebral discs and concomitant pigmentations of the sclera and ear pointed to the possible diagnosis of ochronosis (alkaptonuria).

Our patient responded to targeted questions on his family and personal history and revealed that his brother had suffered from similar back pain for more than 20 years until he died of a heart attack due to a severe coronary artery disease and aortic valve stenosis at the age of 65. He also mentioned that they had both observed black discoloration of their urine since their childhood. With alkaptonuria being the most likely diagnosis, he was subjected to ultrasonography of kidneys and urinary tract which did not

suggest nephrolithiasis and echocardiography where no valvular abnormality was revealed.

In order to establish the diagnosis, we examined the patient's urine, firstly for colour changes -the fresh urine sample was normal in colour and became dark an hour later- and secondly for HGA presentation by the method of gas chromatography. The HGA urine concentration was 27,3

mmol/mmol of creatinine (normally is not detected and in alcaptonurics the average is 3,12 mmol/mmol of creatinine).

We decided to treat the patient with analgesic therapy and vitamin C, 1g daily. Physiotherapy and dietary restrictions with diet low in tyrosine and phenylalanine were also recommended. Despite some reduction in pain, after 6 months of conservative therapy, vitamin C and low protein dietary were not very effective to change the quality of the patient's life.

Discussion

Alkaptonuria is a very rare inborn error of amino acid metabolism due to deficient homogentisic acid (HGA) oxidase enzyme leading to accumulation of HGA in plasma, cartilage, other tissues of human body and its excretion in urine^{13,14}. It has both systemic and peripheral signs and symptoms. Alkaptonuria as a systemic disorder may have other systemic involvement such as cardiac valvular disease or nephrolithiasis other than connective tissue and joint involvement usually present in late middle age^{3,15}.

Our patient presented in his early 80s with no systemic manifestation but he had a long standing history of low back pain and progressive stiffness which is common amongst alkaptonurics. In fact, alkaptonuria is often misdiagnosed as severe degenerative axial and peripheral arthropathy (osteoarthritis) or ankylosing spondylitis^{16,17}. Degenerative spondylosis may be seen along the whole of the spine however the most prominent involvement is in the lumbar region^{15,18}. Tendon thickening and tears and joint effusions usually present later than 30 years of age², as was the story with our case.

Specific findings such as discoloration of the ear cartilage and triangular pigmentation of the sclera combined with the information about dark urine further suggested the diagnosis of alkaptonuria. Non-articular features of ochronosis include bluish discoloration of the ear pinnae, triangular pigmentation of the sclera, and pigmentation over the nose, axillae, and groin and become evident after 30 years of age¹⁷. Our patient had the characteristic pigmentations since his 40s.

Another feature of the disease is prostatic calculi, also common in men- and cardiac murmurs, due to deposition of pigment in cardiac valves^{17,19}. Nephrolithiasis and mitral and aortic valvular calcification and regurgitation usually present in late middle age³. Increased urine concentration of HGA confirms the diagnosis.

Kara et al²⁰ summarized the current treatment options including NSAIDs and preparations containing glucosamine and chondroitin sulfate, intra-articular injections of hyaluronic acid and steroids, arthroscopic debridement of the affected joint and arthroplasty^{2,20}. Currently there is no established therapy or prophylactic treatment of alkaptonuria. Treatment is generally supportive and aiming at preventing or minimizing the effects of ochronotic arthropathy. The antioxidant properties of vitamin C have been shown to help slow the conversion of HGA to its pathologic polymeric intermediate¹⁶.

Dietary restrictions of food containing tyrosine and phenylalanine have been shown to be effective in limiting symptoms of ochronotic arthritis by reducing the production of HGA²¹. Although dietary restriction may be effective in children, it has not shown any benefits in adults^{3,15,22}. Physical therapy along with NSAID has been successful in improving the symptoms but has not been shown to affect the progression of the underlying disease.

Alternative therapies generally are aimed at reducing HGA production in the liver, replacing the enzyme via liver transplantation, or inhibiting the production of HGA through the administration of Nitisinone^{23,24}. Nitisinone is an herbicide that inhibits 4-hydroxyphenylpyruvate dioxygenase an enzyme responsible for the conversion of 4-hydroxyphenylpyruvate to HGA^{24,25}. It is currently used to treat type 1 hereditary tyrosinemia and its oral administration in ochronotic patients has been shown to decrease urinary HGA secretion. N-acetyl cysteine and vitamin E are being investigated for their demonstrated ability to counteract polymerization and accumulation of HGA in vitro. Probably the ideal therapy would be replacing the missing enzyme as an enzymatic protein or replacing the gene as well.

We decided to treat our patient with analgesic therapy paracetamol and gabapentin 300mg x 3/day, vitamin C 1 g daily, dietary restriction of food protein, especially tyrosine and phenylalanine. The patient's back pain improved considerably in the following 6 months but this treatment was not effective enough to stop the rapid progression of the degenerative arthropathy.

In conclusion, although alkaptonuria is a very rare disease, it should be considered when evaluating low back pain, especially if it is combined with degenerative arthritis in elderly patients. The careful observation of possible ochronotic pigmentation, the detailed history of the patient which may reveal darkening of the urine and the pathognomonic radiological studies will help physicians to establish the correct diagnosis. The rapid progression of the ochronotic arthropathy necessitates the immediate treatment of this metabolic disease so as the degenerative arthropathy will be reduced. Replacing the missing enzyme or the gene consists of a very promising future therapy.

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