Aortic valve disease as a first manifestation of Alcaptonuria in surgically treated patient.

Case report

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Aortic valve disease as a first manifestation of Alcaptonuria in surgical treated patient. Case report

BACKGROUND: *Alcaptonuria, a rare metabolic disorder (1:250 000), is usually presented with symptoms such as arthropathies of weight bearing joints.*
CASE REPORT: *In this case, a 65 year old woman was admitted to our hospital with severe aortic stenosis and no other symptoms that would suggest the existance of Alcaptonuria. Intraoperative findings of black discoloration of the affected valve and ascending aorta, pointed towards the diagnosis of cardiac ochronosis, what was then confirmed by a PH examination.*
CONCLUSION: *This case suggests that although alcaptonuria is a slow progressive disease with cardiac ochronosis as a predictable late complication, it can nevertheless be a first sign. In that case the attention should be brought to the surely affected lumbar spine and weight bearing joints, and other connective tissue.*

KEY WORDS: Alcaptonuria, Aortic valve, Cardiac ochronosis, Surgery

Introduction

Ochronosis is a rare inherited metabolic disorder (1:250000) of tyrosine metabolism due to deficiency of homogentisic acid oxidase characterized by homogentisicaciduria, ochronosis and arthritis. The transmission is autosomal recessive and unusually higher frequency (1:19000) is reported in some parts of Slovakia and Dominican Republic [1]. In childhood homogentisicaciduria (alkaptonuria) seen as the staining of the diapers is the only symptom so it can be easily overlooked [2]. Accumulation of homogentisic acid (HGA) and its metabolites in connective tissue causes ochronosis with pigmentation of cartilagineous structures, bone and joint destructions and degenerations of cardiac valves [3]. The most common clinical signs are darkening of the urine after exposure to the air, ocular and cutaneous blue-black pigmentations and arthropathies of weight bearing joints. Symptoms usually become evident about the age of forty. Arthropathy occurs in almost all patients in the third or fourth decade of life starting with symptoms in the knee, hip, shoulder or lumbar spine, often necessitating joint replacement [4]. Currently there is no effective therapy for the disease. High doses of ascorbic acid may prevent deposition of the ochronotic pigment. Low protein diet especially low in phenylalanine and tyrosine is advocated. A new medicine Nitisinone that inhibits the enzyme

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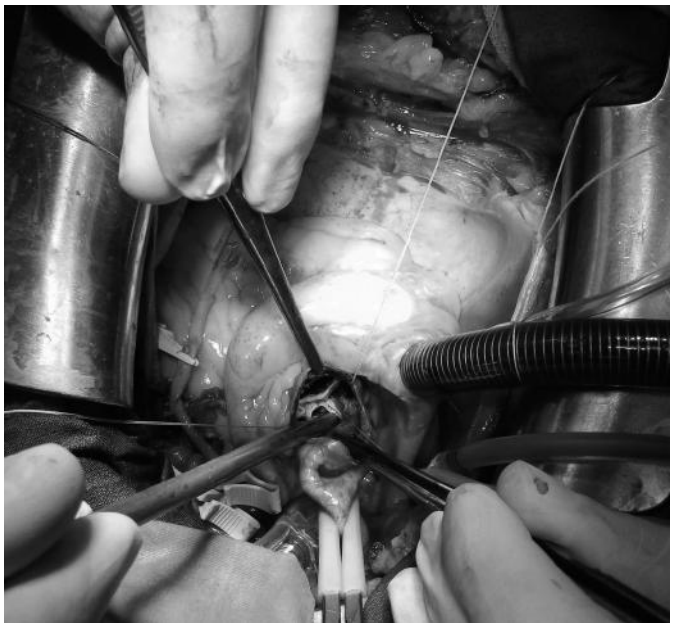

Fig. 1

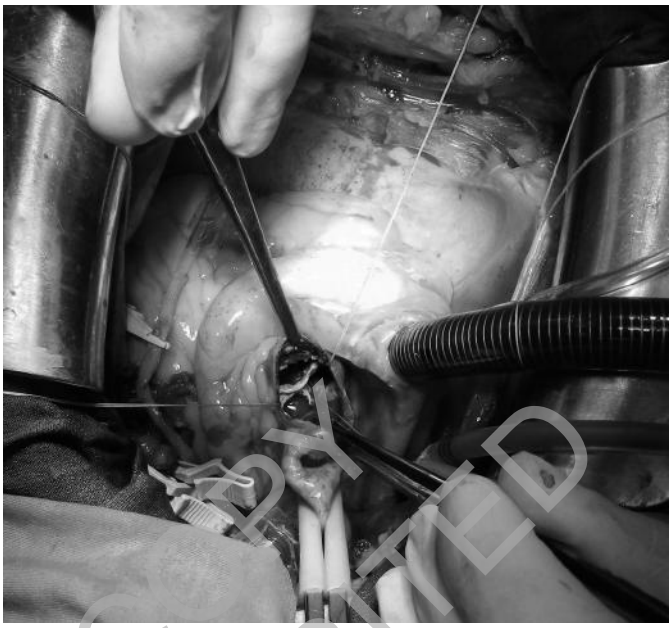

Fig. 2

which produces HGA is on trial for the evaluation of long-term therapy [5].

In adults there is a high incidence of heart disease with symptoms starting at the age of 55. Aortic and mitral valve are usually affected followed by coronary ochronotic deposits. Pathological findings reveal intracellular and extracellular ochronotic deposits in valvular tissue with secondary calcifications [6].

Case Report

A 65-year-old female patient with signs and symptoms of severe symptomatic aortic stenosis was admitted for elective aortic valve replacement. The renal function of this patient was normal and there was no history of renal calculosis, low back pain or other joint affections. She underwent histerectomy in 1995.

Routine laboratory tests were normal including urea and creatinine levels. Echocardiographic findings demonstrated severely calcified aortic valve leaflets with a mean aortic valve gradient of 83 mmHg and calculated aortic orifice area lesser than 1 cm^2. Left ventricular function was normal. Cardiac catheterization showed normal coronary arteries.

The patient underwent aortic valve replacement with a 19 mm mechanical aortic valve (St. Jude Medical, 19mm HP Masters Series Valve). Intraoperatively it was found black discoloration of both ascending aorta and stenotic aortic valve which aroused suspicion of ochronosis. There were no significant calcifications of ascending aorta and coronary arteries. Total bypass time was 102 min. and the valve was replaced in usual manner. The patient made an uneventful recovery and was discharged from hospital without any complications on the 8th postoperative day. Pathohistological examination of aortic cusps revealed the sclerotic change with hyalinization and calcification with deposits of ochronotic pigment. Five years later she is still free from any symptoms related to the cardiovascular system.

On the other hand, in the years after her AVR she slowly started to develop cutaneous and sceletal system symptoms. In particular, her sclerae and ear lobes became dark bluish and she started to complain about the low back pain, which was progressive in nature. Afterwards she fully developed arthritis of hips, knees and thoracolumbar spine with calcifications of intervertebral cartilages. The patient is now wheelchair dependent with high degree of thoracolumbar kyphosis.

Discussion

Alcaptonuria was first described in 1584. by Scribonius but Virchow after observing the pigment microscopically termed the condition Ochronosis [7]. It is a rare autosomal recessive genetic disorder of tyrosine metabolism, which results in the accumulation of homogentisic acid in the connective tissue. This accumulation is initially dealt with by increased renal excretion [8]. From the early childhood increased level of homogentisic acid in the urine leads to urine darkening after a few hours due to oxidation of HGA. It usually leaves dark stains on the diapers, but it is not uncommon to overlook these changes especially with modern plumbing or frequent diapers change. With time there is a gradual tissue deposition, which eventually leads to various symptoms and complications. A diet low in phenylalanin and tyrosine

is recommended together with high doses of ascorbic acid although these measures have not been proved efficient. A new drug, nitisinone is under clinical trials.

The disease is usually latent until the third to fifth decade. Mostly involved is the musculoskeletal system with the development of spondylosis and the arthritis of weight bearing joints (knees, hips and occasionally the shoulders) [9]. These changes usually lead to the need for joint replacement in the mean age of 55. By external examination it can be noticed the blue-black pigmentation of the sclera, ear cartilage and skin to various degrees. Renal involvement with nephrolithiasis is not unusual.

Cardiovascular ochronosis appears lately, usually after the fifth decade of life. Besides pigment deposits in the walls of the aorta and its branches, the aortic valve is the most commonly affected. The pathologic findings show pigment deposits with the calcifications close to the annulus, which usually results in the aortic stenosis. The margins of the leaflets are characteristically spared [10,11]. The involvement of mitral and pulmonary valve is much less common. Microscopical studies show that the pigment deposits are extracellular and with other changes suggestive of cellular death it was postulated that the death of pigment-laden cells was followed by dystrophic calcification with subsequent valve stenosis. The pigment deposits in the elastic and muscular arteries are predominantly in the intima and media and whether this predisposes the patient to early atherosclerosis is still a question. The incidence of coronary arteriosclerosis seems not to be increased by alcaptonuria as is shown in recent study that evaluated the natural history of 58 patients with alcaptonuria [3].

Although the number of alcaptonuric patients, which developed cardiovascular ochronosis of the degree that required surgical intervention is very small, it seems that in the past decades it has an increasing tendency. The reasons for this observation may be the more active life of these patients in the older age than it was before, due to the advancements in the orthopedic surgery.

Including our patient 14 cases of surgically treated cardiovascular ochronosis were reported in the literature to the moment. There were nine males and five female patients with the average age of 66. This correlates with the study of Phornputhul and al. who observed more rapid course of the disease in men although the distribution of alcaptonuria through the gender was equal.

Thirteen of reported patients (92%) underwent aortic valve replacement. In eleven patients the indication was significant aortic stenosis and in two aortic insufficiency [12]. There was only one case of the mitral valve involvement with severe regurgitation that required valve repair along with aortic valve replacement [13]. Although the aortic valve pathology is almost exclusively the reason for surgical treatment other valves must not be overlooked. Of these 14 only 4 patients were aware of their disease since childhood and in 6 of them (43%) the diagnosis of alcaptonuria was established after the operation. So despite the changes in the urine color and the involvement of other systems especially musculoskeletal, the disease can go unnoticed through the adult age until the development of cardiovascular symptoms. And as we can see this situation is far from rare. In all of these 6 patients the first unusual intraoperative finding was the black pigmentation of the sternum, costal cartilages and/or aorta, so in that case the surgeon should remind himself of this rare disease [14]. Although there are some reports of very severe calcifications of both aortic valve and aortic root that made surgical intervention challenging, our impression is that the valve replacement can be done in the usual manner [15]. Of course, heavy pigmentation and uncommon light reflection can make things harder.

Coronary artery disease that required concomitant CABG was reported in 5 patients [16]. It is controversial whether the changes on the coronary arteries are accelerated by the disease or the pigmentation of atherosclerotic plaques is secondary process. Especially in regard that most patients were males in the seventh decade of life.

Considering the involvement of other systems, 11 of these 14 patients (78%) had spondylosis or arthritis of one or more big joints and five of them underwent joint replacement previously. In 9 cases (64%) there were visible cutaneous and scleral pigmentations [17]. But kidney stone was diagnosed only in one patient.

As mentioned earlier, despite uncommon and bizarre look of the black aorta there should not be any inconveniences in the operative work [18]. On the other hand, since all of these patients need aortic valve replacement, there is a question of the choice of the valve. Whether the alcaptonuria would lead to the increased degeneration of the biological valve is not known so we recommend usage of the mechanical prosthesis except for very old patients.

Conclusion

Ochronosis is a slow progressive disease that affects connective tissue. With the advancements in orthopedic surgery cardiac ochronosis is becoming unmasked in older still active patients. Also it is not unusual that the aortic stenosis appears as a first sign of the disease. Surgical procedures in these patients follow the standard techniques. All patients, but especially those previously not aware of the disease should be referred to the orthopedic surgeon. In the follow up it is the spondilosis and arthropathy that mostly affects the quality of life of the patients with ochronosis. Bioprosthesis durability in these cases is still to be determined.

Riassunto

L'alcaptonuria è una rara malattia genetica su base metabolica, che coinvolge una bassa percentuale della popo-

lazione (1:250 000), che abitualmente si manifesta clinicamente con i sintomi di una artropatia, specialmente in soggetti sovrappeso.
Il caso presentato è quello di una donna di 65 anni ricoverata per una grave stenosi valvolare aortica e nessun altro sintomo che potesse suggerire l'esistenza di un'alcaptonuria. In reperto intraoperatorio di una colorazione nerastra della valvola aortica e dell'aorta ascendente orientava verso la diagnosi di ocronosi cardiaca, confermata poi dall'esame anatomopatologico.
Il caso descritto suggerisce che sebbene l'alcaptonuria è una malattia a progressione lenta che può comportare l'ocronosi cardiaca come complicazione tardiva, cinonostante tale rilievo può rappresentare un primo segno della patologia. L'attenzione avrebbe potuto essere rivolta preoperatoriamente alle alterazioni della colonna spinale ed alle articolazioni maggiormente esposte al carico corporeo oltre che agli atri tessuti connettivi.

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Commento e Commentary

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Alcaptonuria, despite its rarity, is a well known pathological condition, characterized by the presence in ecces in the urine of homogentisic oxide, known as alcaptone.
The pathological description dates back to 1865 with the work of Rudolf Virchov, who for the color assumed by a series of internal tissues, such as cartilage, tendons, inner layer of blood vessels, gave it the denomination of ochronosis. Also at the body surface is possibly to detect the condition for an eventual brownish coloration of sclerae, and a brownish discoloratio especially in locations most exposed to sweat, such as the armpits on skin level .
It was B.N. Le Duc in 1858 that recognized its pathogenesis as an expression of a congenital metabolic defect of enzymatic metabolism of two amino acids, tyrosine and phenylalanine, which determines the accumulation in the blood of alcaptone, oxidation of homogentisic acid.
The observation of the authors, doesn't therefore refer to an unknown pathological condition, but adds knowledge of anatomical and morphological remarks in vivo, in the cardiovascular system, thanks to modern cardiac surgery, as had already happened in orthopedics, especially in toraco-lumbar spine and joints more susceptible to the load, besides the autoptic observations. It remains to confirm whether the ochronosis of cardiac valve may represent a pathogenic role in valvular heart disease, or lead to a structural defect in the aortic arch that would become more exposed to the risk of aneurysmal dilatation, or if everything is resolved only in the pigmentary alterations. The rarity of observations makes it difficult to answer the question that remains, therefore, entrusted to future observations.

* * *

L'alcaptonuria, pur nella sua rarità, non rappresenta una condizione patologica ignota, caratterizzata dalla presenza nelle urine dell'ossido dell'acido omogentisico, noto come alcaptone.
La descrizione del quadro patologico risale addirittura al 1865 ad opera di Rudolf Virchov, che per il colore assunto da una serie di tessuti interni, come cartilagini, tendini, intima dei vasi sanguigni, la denominò ocronosi. In superficie corporea è possibilmente rilevabile tale colorito brunastro a livello delle sclere, della cute specie nelle sedi maggiormente esposte al sudore, come le ascelle.
Fu B.N. Le Duc nel 1858 che ne riconobbe la patogenesi quale espressione di un difetto metabolico congenito del metabolismo enzimatico di due amminoacidi, la tirosina e la fenilalanina, che determina l'accumulo nel sangue dell'alcaptone, ossido dell'acido omogentisico.
L'osservazione degli Autori, non si riferisce dunque ad una condizione patologica ignota, ma aggiunge conoscenze non solo morfologiche ma anche anatomopatologiche in vivo, a livello cardiovascolare, grazie alla moderna cardiochirurgia, come era già avvenuto in ambito ortopedico specialmente a livello della colonna vertebrale e delle articolazioni maggiormente soggette al carico e nelle autopsie. Resterebbe da confermare se l'ocronosi valvolare cardiaca può rappresentare un ruolo patogenetico nella valvulopatia, o determinare un difetto strutturale a livello dell'arco aortico che diventerebbe maggiormente esposto al rischio di dilatazioni aneurismatiche, oppure se tutto si risolve nella sola alterazioni pigmentaria. La rarità delle osservazioni rende difficile risolvere il quesito, che resta dunque affidato a future osservazioni.