MedCrave
Step into the World of Research

Journal of Cardiology & Current Research

Black Heart at Surgery - Primary Diagnosis of Alkaptonuria at Surgery

Abstract

Alkaptonuria is a rare genetic disorder of tyrosine catabolism in which homogentisic acid accumulates leading to ochronotic deposition in connective tissue. This has widespread effects including degenerative arthritis and, more rarely, cardiovascular manifestations, the most common of which is aortic stenosis. We present a 66-year old patient in whom we diagnosed alkaptonuria during an aortic valve replacement for symptomatic aortic stenosis. We conducted a world literature review to examine the evidence for the prevalence of aortic valve disease and cardiac involvement in alkaptonuria. We discuss the pathogenesis of aortic valve ochronosis.

Keywords: Aortic valve; Valve stenosis; Alkaptonuria; Valve replacement; Surgery

Case Report

Volume 9 Issue 5 - 2017

Anthie Karavaggelis, Christopher Young and Rizwan Attia*

*Anthie Karavaggelis, Christopher Young and Rizwan Attia**

***Corresponding author:** Rizwan Attia, Department of Cardiothoracic Surgery, St. Thomas' Hospital, 6th Floor East Wing, Westminster Bridge Road, London SE1 7EH, UK, Tel: +44 (0) 2071882014; Fax: +44 (0) 2071881006; Email: rizwanattia@doctors.org.uk

Received: August 30, 2017 | **Published:** August 31, 2017

Introduction

Alkaptonuria is a very rare autosomal recessive genetic disorder of tyrosine catabolism affecting between 1 in 250,000 and 1 in 1 million births [1]. The highest incidence occurs in Slovakia and the Dominican Republic, where incidence reaches 1 in 19,000 births. It is caused by a discrete mutation in chromosome 3q21-3q23, leading to a deficiency in the homogentisate 1, 2 dioxygenase (HGO) [2]. This in turn leads to an accumulation of homogentisic acid (HGA) which is excreted in the urine, accounting for the dark colour which occurs on standing, and the deposition of melanin-like oxidised HGA-derived polymers in connective tissue. The pathological pigmentation that occurs as a result is termed ochronosis.

Alkaptonuria typically presents as a triad of homogentisic aciduria, ochronosis and degenerative arthritis. There is a wide clinical variability in presentation that can be explained by the 84 different mutations found so far. There are also varying differences in rates of renal clearance. The disease usually manifests late in life after the 4th decade due to decline in renal clearance with age. Rarely, alkaptonuria can have cardiovascular manifestations: with ochronosis described in the heart valves, aorta, pericardium, endocardium and coronary arteries [3-5]. Aortic stenosis is the most commonly reported cardiovascular manifestation with a number of case series describing an increase in the prevalence of aortic stenosis compared to the general population.

Case

A 66-year old ex-smoker who presented with gradual deterioration with dyspnoea (NYHA II) that developed over 3-years. Past medical history included hypertension and hypercholesterolaemia. Examination was unremarkable apart from an ejection systolic murmur. A transthoracic echocardiogram confirmed a calcified aortic valve with severe aortic stenosis (EOA 0.7cm^2, MG 53mmHg), mild aortic regurgitation (vena contracta 0.3cm) (Figure 1) and severe three-vessel disease involving the left main stem, the ostial and distal left anterior descending and mid circumflex and distal right coronary artery. His haematological investigations revealed only a minimally raised ESR (43mm/hour). His Logistical Euroscore II was 1.1%. He underwent an elective tissue aortic valve replacement using a 25mm Perimount Magna Ease bioprosthesis and coronary artery bypass grafting. This involved the left internal mammary artery grafted to the left anterior descending and a saphenous venous graft to the intermediate and right coronary artery. On sternotomy he was found to have a completely black aorta, aortic valve and heart (Figure 2). Histological analysis of aortic wall and leaflet tissue diagnosed alkaptonuria (Figure 3). Patient had a good post-operative recovery and on discharge was referred to clinical geneticists for further testing. He remains well on 2-year follow-up.

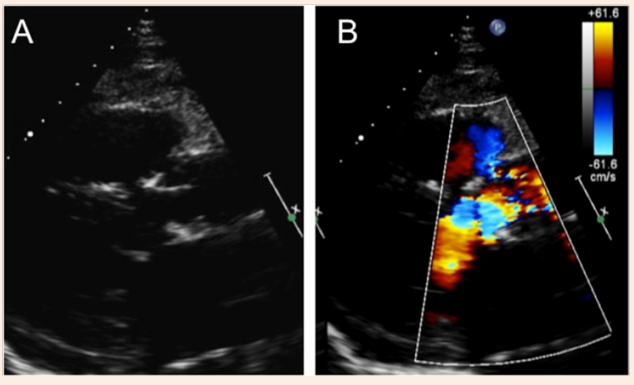

Figure 1: Parasternal long axis transthoracic echocardiogram (A) demonstrating thickened aortic valve leaflets with a stenotic valve on colour flow Doppler (B).

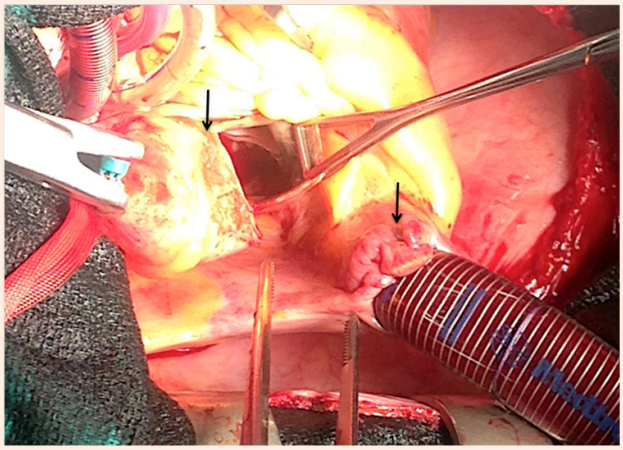

Figure 2: Intraoperative photo demonstrating the opened ascending aorta with the aortic valve exposed. There are pigmented deposits present on the aortic wall and right atrium (arrows) adjacent to the venous drainage line for the cardiopulmonary bypass.

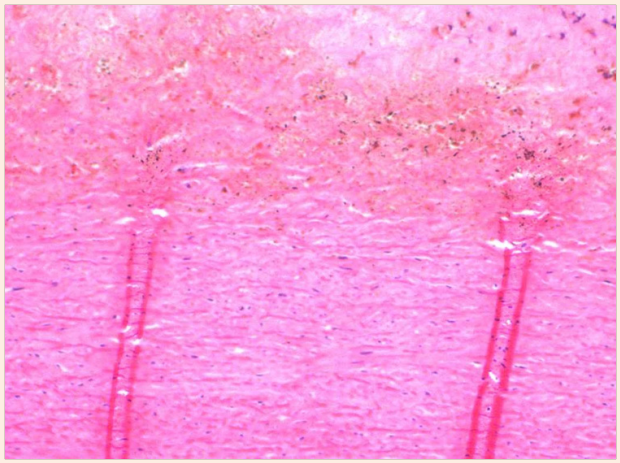

Figure 3: A H&E stained aortic wall histology slide at x20 magnification demonstrating the black pigmentation present in the tunica media and adventia.

Discussion

An increased prevalence of aortic valve disease, and in particular aortic stenosis, is seen in patients with alkaptonuria compared to the general population [6]. In the Cardiovascular Health Study, which looked at 5621 patients aged 65 or older, 1.8% were found to have aortic stenosis [7]. A series of 76 patients with alkaptonuria found aortic stenosis in 25% of patients over 65 [3]. Interestingly, unlike degenerative calcific aortic stenosis, the presence of stenosis was not correlated with the standard cardiovascular risk factors or age related calcification but was moderately correlated with the extent of joint involvement, another manifestation of alkaptonuria where homogenstisate is deposited in the connective tissue within cartilage. Another smaller study of 16 patients found that 50% had aortic valve disease after the 6th decade of life [8]. In our contemporary review of world literature there are 175 patients with alkaptonuria, of whom 35% exhibited aortic valve disease, with 19% stated as aortic stenosis, 11% as aortic regurgitation and 5% as aortic valve disease or aortic valve replacements for unspecified reasons (Table 1).

Table 1:

Article Name	Journal	Type, Level of Evidence	Patient Number	Cardiac manifestation	Outcome/Comments
Alkaptonuria-associated aortic stenosis [6]	Journal of Cardiac Surgery	Case Series & Literature Review	2	AS & CAD	Bioprosthetic AV replacement & CABG
		Level 4		AS	Bioprosthetic AV replacement
A case of alkaptonuria with fatal cardiovascular disturbance (Tsunashima et al. 1976)	Acta Medica Okayama	Case Report	1	AR, AF	Death
		Level 5		Right Heart Failure	
Alkaptonuria- a review of surgical and autopsy pathology [4]	Histology	Case Report and Literature review	1	Asymptomatic AS, mild MV dysfunction	Died from disseminated ovarian cancer, on warfarin for cardiovascular disease
		Level 5			
Alkaptonuria and aortic stenosis (Vlay & Hartman 1986)	Annals of Internal Medicine	Case Report (letter)	1	AS with calcification of aortic root & coronary sinuses	Mechanical AV replacement
		Level 5			

Alkaptonuric aortic stenosis (Roser et al. 2007)	The European Society of Cardiology	Case report Level 5	1	Severe AS	Cardiac catheterisation. Further details not given
Alkaptonuric Ochronosis with Aortic Valve and Joint Replacements and Femoral Fracture (Fisher et al. 2004)	Clinical Medicine & Research	Case study and literature review Level 5	1	Severe AS + minor CAD	Pericardial AV replacement
Aortic stenosis and cardiovascular disease in Alkaptonuria. Case report (Ríos et al. 2010)	Revista Española de Cardiología	Case report Level 5	1	Severe AS + CAD	Mechanical AV replacement + CABG
Aortic Stenosis and Coronary Artery Disease caused by Alkaptonuria, a Rare Genetic Metabolic Syndrome (Vavuranakis et al. 1998)	Cardiology	Case report Level 5	1	Severe AS + severe CAD	AV replacement
Aortic Valve Stenosis in Alkaptonuria (Hangaishi et al. 1998)	Circulation	Case report Level 5	1	Severe AS with congestive heart failure	Bioprosthetic AV replacement
AS and vascular calcifications in alkaptonuria [3]	Molecular Genetics and Metabolism	Retrospective Cohort Study? Case Series?	76	6- AV replacements	No correlation found between the severity of CV manifestation and standard CV risk factors or with urine HGA levels
		Level 3		12 –aortic sclerosis	Pts with alkaptonuria who had at least one ECHO were enrolled
				7 – aortic stenosis (4 mild, 2 moderate and 1 severe) 12 – mild AR	
				Of 40 CT, 17 suitable for evaluation of vascular calcification:	
				3 – sig coronary calcification	
				8 – vascular calcification (3 severe)	
Aortic valve ochronosis: a rare manifestation of alkaptonuria (Steger, 2011)	BMJ Case Reports	Case report Level 5	1	Severe AS	Bioprosthetic AV replacement
Aortic valve replacement for aortic stenosis caused by alkaptonuria (Hiroyoshi et al. 2013)	The Annals of Thoracic Surgery	Case report Level 5	1	Severe AS	Bioprosthetic AV replacement
Alkaptonuria: A case complicated with valvular heart disease and immunodeficiency (Mori et al. 1994)	Internal Medicine	Case report Level 5	1	Moderate AS, mild MR, moderate AR	Not discussed

Black aorta: a rare finding at aortic valve replacement [14]	Journal of Invasive Cardiology	Case report Level 5	1	Moderate MR, moderate AS, moderate-severe AR CAD Focal aortic dissection	AV replacement + CABG
Black aorta in a patient with alkaptonuria (ochronosis) (Concistré et al. 2011)	Journal of Cardiovascular Medicine	Case report Level 5	1	Severe AS	Mechanical AV replacement
Black aortic valve ochronosis (Laco et al. 2008)	Acta Pathologica Microbiologica et immunologica scandinavica	Case report (letter) Level 5	1	Severe AS & mild combined MR & MS	Mechanical AV replacement
Bluish-black pigmentation of the sclera and the aortic valve in a patient with alkaptonuric ochronosis (Wilke et al. 2010)	Herz	Case report Level 5	1	AR, MR, TR	AV replacement
Cardiac ochronosis valvular heart disease with dark green discoloration of the leaflets (Erek et al. 2004)	Texas Heart Institute	Case report Level 5	1	Severe AS, moderate MR	Bioprosthetic AV replacement and mitral valve annuloplasty
Cardiovascular manifestations of alkaptonuria (Pettit et al. 2011)	Journal of Inherited Metabolic Disease	Case series Level 4	16	6 had severe aortic valve disease: 2 mild AS 1 mild AS & moderate AR 1 moderate AS & mild AR 2 aortic sclerosis 2 mitral valve thickening not associated with disruption	At time of this investigation where patients with alkaptonuria underwent several cardiovascular investigations, no patient had a prior history of valvular disease & 1 patient had prior CAD
Natural history of alkaptonuria [1]	New England Journal of Medicine	Case series Level 4	58	3 pts had aortic-valve replacement. No patient had coronary-artery calcification before the age of 40years, but 50 percent had computed tomographic CT evidence of coronary-artery calcification by the age of 59.	There was no correlation between coronary-artery calcification and an elevated serum cholesterol level.

Citation: Karavaggelis A, Young C, Attia R (2017) Black Heart at Surgery - Primary Diagnosis of Alkaptonuria at Surgery. J Cardiol Curr Res 9(5): 00335. DOI: 10.15406/jccr.2017.09.00336

Alkaptonuric Aortic Stenosis: a case report (Gonzales 1997)	American Association of Nurse Anaesthetists Journal	Case report Level 5	1	Severe AS, Congestive Heart Failure, mild CAD	Emergency AVR with Dacron patch, treatment in ICU, death
Aortic Regurgitation in Alkaptonuria (Yoshikai et al. 2004)	The Journal of Heart Valve Disease	Case report Level 5	1	Severe AR, mild AS and CAD in RCA, fibrous strand tethered to left coronary cusp (thought to be unrelated to AR)`	Mechanical AVR, CABG
Aortic valve stenosis due to alkaptonuria (Brueck et al. 2008)	The Journal of Heart Valve Disease	Case report Level 5	1	Severe AS, CAD	Bioprosthetic AVR, CABG
AS in alkaptonuric ochronosis (Cercek et al. 2002)	The Journal of Heart Valve Disease	Case report Level 5	1	Severe AS	AVR
Ochronosis: an unusual finding at AVR (Helou et al. 1999)	The Canadian Journal of Cardiology	Case report Level 5	1	Severe AS, CAD	AVR, 3 vessel bypass
Ochronosis and Alkaptonuria: report of a new case with calcified aortic stenosis (L.Dereymaekeret al. 1989)	Acta Cardiologica	Case report Level 5	1	Severe AS	Mechanical AVR
Ochronosis of the AV and Aorta (Kovacevic et al. 2006)	The Journal of Heart Valve Disease	Case report Level 5	1	Severe AS, CAD	Mechanical AVR, CABG

Autopsy studies and case series have also linked alkaptonuria with coronary artery calcification. In particular, an increase in ochronotic deposition in the fibrous caps and lipid cores of atheromatous plaques has been described [9,10]. A large study of 58 patients with alkaptonuria found that 50% of patients over the age of 59 had CT evidence of coronary artery calcification. There is however no independent association of alkaptonuria increased susceptibility to clinically significant atheroma [1].

The pathogenesis of the cardiac manifestations in alkaptonuria is unclear, however, several theories have been proposed. It is thought that the ochronotic pigment is first deposited in fibrocytes, macrophages, smooth muscle cells and the extracellular matrix. These pigment-laden cells then degenerate, releasing the pigment extracellularly where it acts either as a chemical irritant, producing a pro-inflammatory reaction, or as a direct enzyme inhibitor which alters cartilage metabolism leading to dystrophic calcification and fibrosis of the cardiac valve leaflets [11,12]. Furthermore, ochronotic deposition has been found predominantly in areas of turbulent flow, where there are eddy currents, such as in the sinotublar junction which normally aids diastolic coronary filling. This might explain the deposition of ochronotic pigment in the ostia of the coronary arteries and aortic valve leaflets, whilst there is minimal deposition in venous circulation. Thus vascular flow dynamics dictate the site of pigment deposition leading to the ensuing microvascular damage [4].

Nitisinone, a potent inhibitor of the second enzyme in tyrosine catabolism, is currently the only treatment effective for reducing HGA levels in alkaptonuria. In a small RCT [13] 18 patients were treated for 3 years and 4 in-control *versus* 1 in the treated group had an increase in aortic valve velocities (>0.3m/s). The authors concluded that it was difficult to draw conclusions from a small study but postulate the effects might be maximised if treatment is started early before significant pigment deposition has occurred, analogous to statin therapy for calcific aortic stenosis [13]. Other studies have reported a dramatic increase in tyrosine levels with nitisinone. This can lead to corneal irritation, dermatological and neurological side effects, and it remains uncertain whether nitisinone provides any long-term benefits [1,14]. An ongoing study to explore age-related differences in toxicity of nitisinone

with a view to optimising therapeutic doses in presymptomatic patients is currently taking place [15]. Attempts to treat alkaptonuria with high dose vitamin C and dietary restriction of tyrosine and phenylamine intake has failed to produce a decrease in HGA levels [16]. Nevertheless, patients with alkaptonuria have a high morbidity but a low mortality with a relatively normal lifespan.

Cardiovascular disease can have a significant impact on patients and thus if patients are diagnosed there is growing consensus that they require echocardiographic screening after the age of 40 to detect valvular heart disease and cardiac gated CT to assess coronary artery calcification. The choice of valve prosthesis also remains unclear in such patients at surgery. There are no reports of early deterioration of bioprosthetic valves in these patients. We consented the patient for tissue valve replacement and were unsure of the diagnosis till confirmed histologically after surgery. Thus we carried out a tissue valve replacement [17,18].

Although cardiac ochronosis is a rare clinical presentation, surgeons should be aware of it as they might be confronted with it as in our case during surgery. They must also investigate and follow patients known to have alkaptonuria as they develop cardiovascular disease at a much earlier age. Timely aggressive intervention and medical treatment are of paramount importance.

Conflict of Interests

None.

Disclosures

None.

References

1. Phornphutkul C, Introne WJ, Perry MB, Bernardini I, Murphey MD, et al. (2002) Natural History of Alkaptonuria. N Engl J Med 347(26): 2111-2121.
2. Fernández-Cañón JM, Granadino B, Beltrán-Valero de Bernabé D, Renedo M, Fernández-Ruiz E, et al. (1996) The molecular basis of alkaptonuria. Nat Genet 14(1): 19-24.
3. Hannoush H, Introne WJ, Chen MY, Lee SJ, O'Brien K, et al. (2012) Aortic stenosis and vascular calcifications in alkaptonuria. Mol Genet Metab 105(2): 198-202.
4. Helliwell T, Gallagher J, Ranganath L (2008) Alkaptonuria - a review of surgical and autopsy pathology. Histopathology 53(5): 503-512
5. Butany J, Naseemuddin A, Moshkowitz Y, Nair V (2006) Ochronosis and Aortic Valve Stenosis. J Card Surg 21(2): 182-184.
6. Lok ZS, Goldstein J, Smith JA (2013) Alkaptonuria-Associated Aortic Stenosis. J Card Surg 28(4): 417-420.
7. Otto C, Lind B, Kitzman D, Gersh B, Siscovick D (1993) Association of Aortic-Valve Sclerosis with Cardiovascular Mortality and Morbidity in the Elderly. N Engl J Med 341(3):142-147.
8. Pettit SJ, Fisher M, Gallagher JA, Ranganath LR (2011) Cardiovascular manifestations of Alkaptonuria. J Inherit Metab Dis 34(6): 1177-1181.
9. Galdston M, Steele J, Dobriner K (1952) Alcaptonuria and ochronosis. The American Journal of Medicine 13(4): 432-452.
10. Skinsnes OK (1948) Generalized ochronosis; report of an instance in which it was misdiagnosed as melanosarcoma, with resultant enucleation of an eye. Arch Pathol (Chic) 45(4): 552-558.
11. Gaines JJ Jr, Pai GM (1987) Cardiovascular Ochronosis. Arch Pathol Lab Med 111(10): 991-994.
12. Resnick D (2002) Diagnosis of bone and joint disorders. (4th edn.), Pennsylvania, USA.
13. Introne WJ, Perry MB, Troendle J, Tsilou E, Kayser MA, et al. (2011) A 3-year randomized therapeutic trial of nitisinone in alkaptonuria. Mol Genet Metab 103(4): 307-314.
14. Goodfellow R, Schwartz J, Leya F (2005) Black aorta: a rare finding at aortic valve replacement. Invasive Cardiology 17(3): 165-167.
15. Nyhan WL (2011) Nitisinone (NTBC) In Different Age Groups Of Patients With Alkaptonuria. A service of the US National Institutes of Health.
16. Mayatepek E, Kallas K, Anninos A, Müller E (1998) Effects of ascorbic acid and low- protein diet in alkaptonuria. Eur J Pediatr 157(10): 867-868.
17. (2000) University of California, San Diego, Nitisinone (NTBC) in different age groups of patients with alkaptonuria. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine, USA.
18. Virchow R (1866) Ein Fall von allgemeiner Ochronose der Knorpel und knorpel Ã¤hnlichen Theile. Archiv f pathol Anat 37(2): 212-219.