Cardiology in the Young (2017), **27**, 1434–1436
doi:10.1017/S1047951117000671

Brief Report

Aortic dissection and cystinosis: is there any relationship?

Masih Tajdini, Mehdi Bayati, Ali Vasheghani-Farahani

Tehran Heart Center and School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract Cystinosis is a rare, autosomal-recessive genetic disorder. The kidneys are commonly involved, as there is cystinosin protein malfunction, and nephropathic cystinosis ensues. Although cardiac and vascular involvements are rare, we describe a unique case of aortic dissection in a 25-year-old female with cystinosis. We discuss the possible aetiologies of aortic dissection in this condition.

Keywords: Cystinosis; aortic dissection; young adult

Received: 4 December 2016; Accepted: 14 March 2017; First published online: 11 May 2017

Cystinosis is a rare, autosomal-recessive, genetic disorder caused by mutation of the Cystinosin Lysosomal Cystine Transporter gene encoding the transmembrane transporter protein cystinosin, leading to excess cysteine accumulation within lysosomes throughout the body, particularly in the kidneys. Nephropathic cystinosis eventually progresses to end-stage renal disease, and there is need for renal transplantation in most of the patients.[1] Common clinical manifestations appear at 3–6 months of life and include polyuria, failure to thrive, growth retardation, developmental delay, rickets, constipation, and acute dehydration episodes.[2] Aortic dilation is an incidental finding in the annual echocardiography of children with end-stage renal disease,[3] but cardiovascular involvement is rare in cystinosis. Restrictive cardiomyopathy due to myocardial cystine deposition has been repoted.[4] Although risk factors for vascular calcification and obstructive atherosclerosis are common in cystinosis patients – end-stage renal disease, hypertension, diabetes, hypercholestrolaemia, and abnormalities of calcium and phosphate homoeostasis – this disease has been considered an independent risk factor for the development of vascular calcifications.[5]

Correspondence to: M. Tajdini, MD, Cardiology Resident, Tehran Heart Center, Tehran University of Medical Sciences, North Kargar Ave., Tehran 1411713138, Iran. Tel: +98 21 8802 9256; Fax: +98 21 8802 9702; E-mail: drmasih84@yahoo.com

Dissecting aortic aneurysm usually affects middle-aged and elderly patients with atherosclerosis and hypertension. In younger patients, aortic dissection is mostly associated with aortic coarctation, genetic disorders such as cystinosis, and/or valvular abnormalities.[6] In this article, we describe a previously rare case of aortic dissection in a 25-year-old female with cystinosis.

Case report

A 25-year-old woman was referred to our department because of acute, severe left hemithorax pain for the past 10 hours, accompanied by nausea. She was a known case of cystinosis, and had undergone renal transplantation because of nephropathic cystinosis complications at the age of 13 years. Her weight and height were 48 kg and 150 cm, respectively. The main skeletal deformity was genu valgum. She had a dilated ascending aorta for the past 5 years, which had been followed-up by echocardiography imaging on a regular basis. In her last echocardiographic study, which was performed 6 months ago, the aortic root dimension was reported to be 46 mm. Her medications included cellcept, sandimon, prednisolone, metohexal, and losartan. During physical examination, the patient was alert and oriented. Her left-arm blood pressure was 130/80, and her right-arm blood pressure was 105/60. She was tachycardic, and her right radial pulse was undetectable. Electrocardiographic tracing

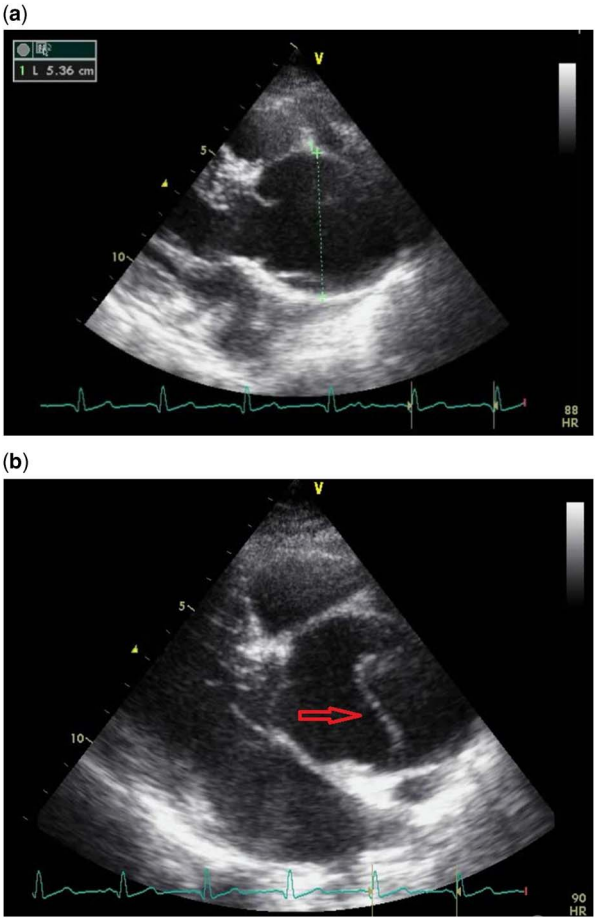

Figure 1.
*Transthorasic echocardiography and parasternal long-axis views: (**a**) dilated ascending aorta and (**b**) dissecting flap in the ascending aorta.*

was normal. On urgent transthoracic echocardiography, she had mild left ventricular hypertrophy with an ejection fraction of 55%. Mild mitral valve regurgitation, tricuspid aortic valve, moderate aortic valve regurgitation, and a spiral dissecting flap in the proximal aorta with mild pericardial effusion were observed (Fig 1). The constellation of findings was in favour of type A aortic dissection based on the Stanford classification.

Urgent vascular surgery consultation was requested, and intravenous medical labetalol was initiated to decrease blood pressure. The patient underwent aortic correction surgery. The tear in the ascending aorta, which caused the dissection, was repaired. Subsequently, the aorta was reinforced with a Dacron graft. After 1 month of follow-up, the patient was symptom-free and in good overall health.

Discussion

Cystinosis is a rare autosomal genetic disorder that involves multiple organs. Cardiovascular involvement is not common in cystinosis. Cardiomyopathy, left ventricular hypertrophy, aortic valve calcifications, and arterial stiffness have been reported as cardiovascular complications in end-stage renal disease.[7] Development of aneurysms in patients with nephropathic cystinosis is a very rare condition. There is only one reported case of a dissecting aneurysm – in a 7-year-old boy in 1979 – in the literature. In this report, a 7-year-old boy with history of cystinosis presented with severe lower-back pain and blood pressure of 200/150. The patient died eventually after a few hours. Autopsy findings revealed a large ruptured dissecting aneurysm of the descending thoracic aorta.[8] In contrast to the cardiovascular system, renal involvement is common and may progress to end-stage renal disease. The mechanism of aneurysm formation in cystinosis is not well understood. Findings suggest that malnutrition, inflammation, and oxidative stress play a role in the development of aortopathy in cystinosis.[7]

Other possible aetiologies could be inflammation and oxidative stress. Chronic aortic wall inflammation increases local expression of proteinases, which leads to degradation of structural connective tissue proteins. Mechanical failure of medial elastin and adventitial collagen leads to aneurysmal dilation and rupture. Inflammatory cells commonly infiltrate the aortic wall. Matrix-degrading enzymes released by inflammatory cells lead to medial degeneration and play a role in dilation and rupture. Haemodynamic stress, ischaemia, autoimmune processes, or extension of intimal atherosclerosis, which are exacerbated in cystiniosis as a result of end-stage renal disease, stimulate the smooth muscle cells, and inflammatory cells may enter the media in response to these signals. Pro-inflammatory cytokines such as tumour necrosis factor-α, interleukin-1 β, interleukin-6, interferon-γ, and matrix metalloproteinases – the most prominent elastin- and collagen-degrading enzymes produced in human aortic aneurism tissue – are released. Matrix metalloproteinases and these pro-inflammatory cytokines degrade the elastin and collagen of the aortic wall. Intimal thickening and atherosclerotic plaques are increased because of end-stage renal disease in cystinosis, and therefore nutrient supply to the media is limited and depends on diffusion from the aortic lumen. Smooth muscle cell apoptosis as a result of medial ischaemia or cellular immune responses has been considered as another factor involved in aortic aneurism.[9]

Secondary hypertension due to end-stage renal disease is another predisposing factor. Approximately 75% of all patients who suffer from aortic dissection have hypertension. Hypertension leads to changes in arterial wall structure, including intimal thickening, calcification, and adventitial fibrosis. These changes may affect the elastic properties of the arterial wall

https://doi.org/10.1017/S1047951117000671 Published online by Cambridge University Press

and increase stiffness, and thereby predispose to aneurysm or dissection. The vast majority of hypertensive patients never suffer from aortic dissection, and therefore hypertension alone is not usually associated with significant aortic root dilation.[10]

Owing to the rare incidence of cystinosis, there are no guidelines on the definite size of the aortic aneurysm, which requires intervention. In other genetic disorders such as Marfan syndrome, surgical intervention is required when the size of the aneurysm reaches up to 5 cm. It seems that cystinosis patients are susceptible to aortic aneurysm and dissection, and should be closely followed-up for development of these complications.

Acknowledgements

The authors would like to express their special thanks to the Cardiology Department staff of Tehran Heart Center, Tehran, Iran.

Financial Support

None.

Conflicts of Interest

None.

Ethical Standards

The study was approved by Tehran University of Medical Science Ethics Committee.

References

1. Shotelersuk V, Larson D, Anikster Y, et al. CTNS mutations in an American-based population of cystinosis patients. Am J Hum Genet 1998; 63: 1352–1362.
2. Nesterova G, Gahl WA. Cystinosis: the evolution of a treatable disease. Pediatr Nephrol 2013; 28: 51–59.
3. Kaddourah A, Uthup S, Madueme P, et al. Prevalence and predictors of aortic dilation as a novel cardiovascular complication in children with end-stage renal disease. Clin Nephrol 2015; 83: 262.
4. Edelman M, Silverstein D, Strom J, Factor SM. Cardiomyopathy in a male with cystinosis. Cardiovasc Pathol 1997; 6: 43–47.
5. Ueda M, O'Brien K, Rosing DR, et al. Coronary artery and other vascular calcifications in patients with cystinosis after kidney transplantation. Clin J Am Soc Nephrol 2006; 1: 555–562.
6. Fikar CR. Acute aortic dissection in children and adolescents: diagnostic and after-event follow-up obligation to the patient and family. Clin Cardiol 2006; 29: 383–386.
7. Groothoff JW, Lilien MR, van de Kar NC, et al. Cardiovascular disease as a late complication of end-stage renal disease in children. Pediatr Nephrol 2005; 20: 374–379.
8. Strayer DS. Cystinosis and a dissecting aortic aneurysm in a 7-year-old boy. Am J Dis Child 1979; 133: 436–438.
9. Golledge J, Norman PE. Current status of medical management for abdominal aortic aneurysm. Atherosclerosis 2011; 217: 57–63.
10. Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. JAMA 2000; 283: 897–903.