A late presentation of Loeys–Dietz syndrome associated with an aortic root aneurysm

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ABSTRACT

Loeys–Dietz syndrome (LDS) is characterised by a mutation in the transforming growth factor beta receptor, and is strongly associated with aortic aneurysms and rupture. Most cases of LDS present in the second decade of life, with the average life expectancy being 37 years. We report a case of suspected LDS (owing to significant family history of the disorder) that presented in the seventh decade of life. Our patient had aortic root dilation and was initially believed to have Marfan syndrome. However, subsequent tests were negative. On further investigation of her family history, it was revealed that she had a strong positive family history of aortic rupture and aneurysms associated with genetically confirmed atypical LDS. By reporting this case, we aim to highlight the importance of considering inherited connective tissue disorders when a patient presents with aortic aneurysms or dissections associated with a strong family history of aortic pathology.

KEYWORDS

Loeys–Dietz syndrome – Aortic root aneurysm – Aortic dissection

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Case history

A 70-year-old woman was referred to her local cardiology centre with a diastolic murmur associated with dyspnoea. She reported no chest pain or fevers. Her past medical history included bronchiectasis, pulmonary embolus and deep vein thrombosis, for which she was on lifelong warfarin. Of particular note, she had a very strong family history of aortic disease and sudden death associated with genetically confirmed Loeys–Dietz syndrome (LDS). Her sister had significant aortic surgery for aortic dissection and her nephew had prophylactic aortic surgery after both had genetic testing that confirmed a diagnosis of LDS. Furthermore, her father's brother and his son had died at young ages from aortic rupture.

On examination, the patient was noted to be tall with a long face and long fingers, and had translucent skin. There was no hypermobility and she had a normal palate. Her heart rate was regular at 90bpm. A diastolic murmur was noticed, loudest at the left sternal edge.

Transthoracic echocardiography (TTE) showed a normal left ventricle with preserved ejection fraction, a bicuspid aortic valve with mild aortic regurgitation and a dilated aortic root measuring 4.1cm. Annual repeat TTE showed no significant enlargement of the aortic root until 2014, when the aortic root diameter measured 4.6cm. Computed tomography coronary angiography showed no evidence of coronary artery obstruction and carotid Doppler imaging was normal (Fig 1).

In 2016 the patient's symptoms deteriorated with sudden onset of worsening dyspnoea and palpitations. She therefore underwent cardiac magnetic resonance imaging, which confirmed an increasingly dilated aortic root of 4.9cm (Fig 2) but there was no evidence of aortic dissection or coarctation. In addition, there was moderate aortic regurgitation. As a result, she was listed for urgent cardiac surgery.

Intraoperative findings included a pseudobicuspid aortic valve with fusion of the left and right coronary cusps, and the aortic root was asymmetrically dilated. The patient underwent a mechanical Bentall procedure using a Carbo-medics Carbo-Seal® Valsalva 23mm valve (LivaNova, Gloucester, UK) and a 26mm graft (replacement of aortic valve with mechanical valve, replacement of aortic root and ascending aorta with composite graft, and reimplantation of the coronary arteries into the composite graft). Her postoperative course was unremarkable and she was discharged home with symptomatic improvement.

Discussion

LDS is caused by an autosomal dominant mutation in the genes coding for the transforming growth factor beta (TGF- β) receptor.¹ It was first described by Bart Loeys, Harry Dietz and colleagues in 2005, and its incidence currently remains unknown. The mutation causes an increase in the signalling of TGF- β , which results in overproduction of collagen,

Figure 1 Three-dimensional image of the dilated aortic root and coronary arteries

Figure 2 Cardiac magnetic resonance imaging at the level of the aortic root showing dilated aortic root of 4.9cm

disarray of elastic fibres and loss of elastin.² Diagnosis is made by molecular testing. Despite the autosomal dominant inheritance pattern of LDS, it is estimated that 75% of mutations are *de novo*, with no family history of the disease.¹ Patients have been noted to usually present with symptoms in the second decade of life, the average life expectancy with LDS being 37 years.¹

Two phenotypes have been described.¹ Type 1 involves a triad of vascular tortuosity and aneurysms, hypertelorism and a bifid uvula or cleft palate. LDS type 2 presents with similar stigmata to Ehlers-Danlos syndrome as well as vascular tortuosity and aneurysms. The most common site for

the development of aortic aneurysms is in the aortic root; aneurysms of the ascending or descending aorta are seldom found. These vascular manifestations are also commonly found with other congenital heart defects, with bicuspid aortic valves being much more common than in the general population.⁵

Patients with LDS are often suspected to have Marfan syndrome and like Marfan syndrome, there is a wide variation in the phenotypic expression of LDS. As a result, some patients may present much later in life.

In all patients with aortic aneurysms or dissection, a detailed family history is extremely important. This should be followed up by careful examination for any stigmata of connective tissue disorders. Genetic counselling and screening is another vital aspect of diagnosis, and specimens should be sent for histopathology at the time of surgery. Our patient underwent deoxyribonucleic acid sequencing and molecular genetic analysis of genes associated with aortic pathology. This confirmed that she was heterozygous for the missense variant of the *TGFBR1* gene. This was the same genetic mutation as that detected in her sister, and it is associated with LDS and familial thoracic aortic aneurysms. Consequently, testing for the *TGFBR1* variant in her offspring was recommended.

These patients should be followed up with yearly imaging from head to pelvis to assess the vascular tree, and they should be discussed and managed in specialist aortic centres. Current guidelines advise elective replacement of the aortic root when the diameter exceeds 4cm or if rapid expansion of more than 0.5cm per year occurs.⁴

Conclusions

Patients with a significant and genetically proven family history of aortic aneurysms and dissections should undergo genetic counselling and testing to identify connective tissue disorders. These patients need regular follow-up review, imaging and multidisciplinary team discussion with the aim being to perform elective surgery to prevent aortic dissection or rupture. Elective replacement of the aortic root is advised when the diameter exceeds 4cm or when there is rapid expansion of more than 0.5cm per year.

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