Loeys-Dietz syndrome: a Marfan-like syndrome associated with aggressive vasculopathy

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ABSTRACT

Loeys-Dietz syndrome is a recently-characterised genetic disorder with an autosomal dominant inheritance due to mutations in the transforming growth factor beta-receptor Type I or Type 2 genes. We present a Chinese female neonate with genetically-confirmed Loeys-Dietz syndrome, cleft palate, hypertelorism, and an early dilatation of the aortic root and ascending aorta. This syndrome is associated with an aggressive arteriopathy, with an increased risk of dissection and rupture. Early diagnosis, close monitoring and early surgery may prolong the life in affected individuals. Losartan is an emerging therapy that may help slow down the rate of arterial dilatation.

Keywords: aortic aneurysm, Loeys-Dietz syndrome, losartan, Marfan syndrome, transforming growth factor beta

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INTRODUCTION

Loeys-Dietz syndrome (LDS) (Online Mendelian Inheritance in Man, #609192) is an autosomal dominant disorder of the connective tissue, recently described in 2005.[1] It was named after Loeys (the first author) and Dietz (the anchoring author) of the original publication. Individuals with LDS exhibit a variety of features, mainly involving the cardiovascular, musculoskeletal and central nervous systems. There is a phenotypic overlap with Marfan syndrome (MFS) and Ehlers-Danlos syndrome. Arterial dilatation, in particular, aortic root dilatation with subsequent dissection or rupture, is a life-threatening complication of this genetic disorder. We describe a case of genetically-confirmed LDS diagnosed in Singapore, and emphasise the early presentation and rapidly-progressive nature of the associated vasculopathy, as compared to other MFS-like disorders. We also reviewed the current literature concerning the genetics, presentation and management of LDS.

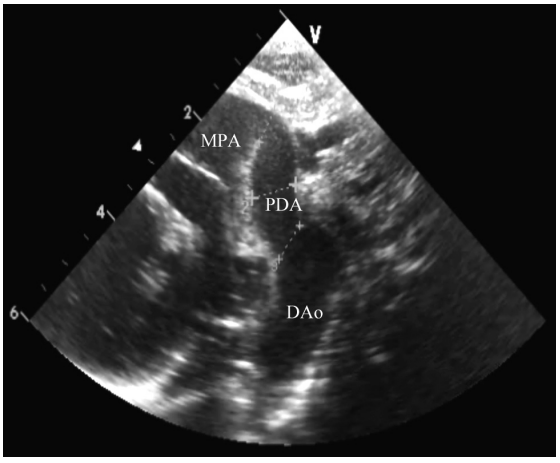

Fig. 1 2D echocardiogram (ductal view) taken on Day 2 of life shows a large patent ductus arteriosus.
MPA: main pulmonary artery; PDA: patent ductus arteriosus; DAo: descending aorta

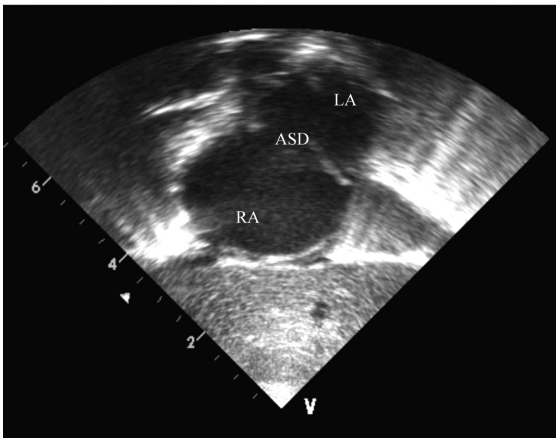

Fig. 2 2D echocardiogram (subcostal view) taken on Day 2 of life shows a moderate secundum atrial septal defect.
LA: left atrium; RA: right atrium; ASD: atrial septal defect

CASE REPORT

A female Chinese neonate was born at 38 weeks' gestation with a birth weight of 3.0 kg. Antenatal ultrasonography screening had revealed cysts on both sides of the cavum septum pellucidum. The parents were non-consanguineous. At birth, the infant was noted to have a posterior cleft palate. There was no cleft lip. There was micrognathia. Both thumbs were hyperextensible; there was bilateral camptodactyly and arachnodactyly. The

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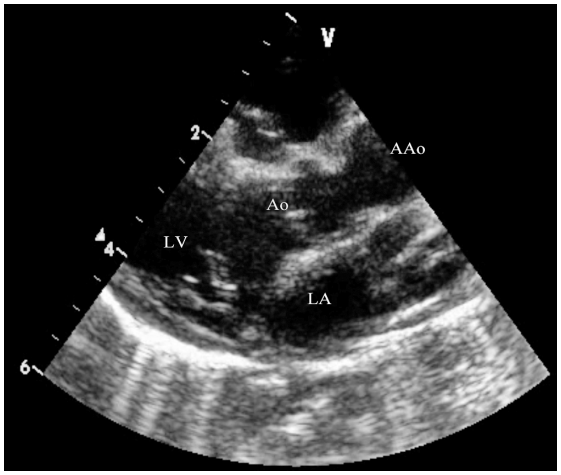

Fig. 3 2D echocardiogram (parasternal long-axis view) shows a dilated ascending aorta. The aortic sinus is also prominent.
LV: left ventricle; Ao: aortic annulus; AAo: ascending aorta; LA: left atrium

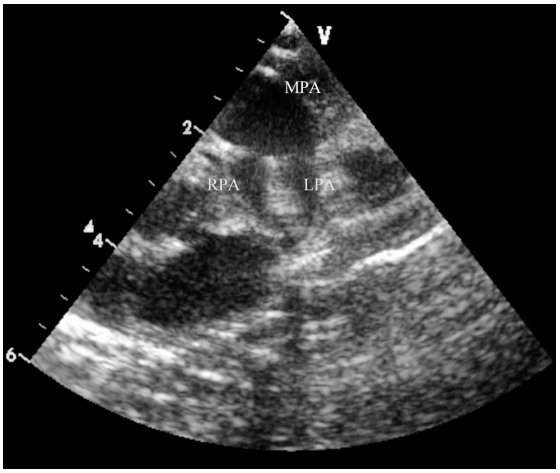

Fig. 4 2D echocardiogram (short-axis view) shows a dilated main pulmonary artery.
MPA: main pulmonary artery; RPA: right pulmonary artery; LPA: left pulmonary artery

right knee and both wrists were subluxed, requiring full casting of the right knee and splinting of both wrists.

There was a cardiac murmur detected on the second day of life, and she was mildly tachypnoeic. 2D echocardiogram showed an extremely large patent arterial duct measuring 6.9 mm × 7.6 mm (Fig. 1). There was a moderate secundum atrial septal defect measuring 8 mm × 10.7 mm (Fig. 2). The aortic annulus measured 10.4 mm, the aortic sinus 12.2 mm, and the ascending aorta 11.9 mm. There was pulmonary hypertension. No ventilatory support was required in the postnatal period. Cranial ultrasonography (US) showed bilateral sub-ependymal cysts measuring 3.5 cm × 0.6 cm on the right and 3.8 cm × 0.9 cm on the left. The intracranial midline structures were intact. Renal US was normal. Eye examination showed nonspecific pigmentation in the right retina. Karyotype analysis showed 46XX. The infant was reviewed by a geneticist, and a diagnosis of distal arthrogryposis was considered.

At two months of age, the baby was noted to have hypertelorism, blue sclera, deep-set eyes, frontal bossing and pectus excavatum. 2D echocardiogram showed mild dilatation of the aortic root and ascending aorta. Based on these features and those present at birth, the diagnosis of LDS was clinically suspected. By five months of age, she weighed 6.4 kg (50th centile) and had a length of 67 cm (90th centile). Her head circumference was 44 cm (> 97th centile). There was a mild gross motor developmental delay. She was just able to roll over. She was unable to sit with support. She was beginning to grasp objects and had a social smile.

Serial 2D echocardiograms showed a reduction in the size of the patent ductus arteriosus and the atrial septal defect. However, the aortic root and ascending aorta were noted to be increasingly dilated (Fig. 3). The aortic annulus measured 12.9 mm, the aortic sinus measured 17.6 mm and the ascending aorta measured 14.5 mm. The main pulmonary artery was also dilated, measuring 18.3 mm (Fig. 4). There was no aortic or pulmonary regurgitation. The rate of dilatation of the ascending aorta is shown in Fig. 5. For comparison, the ascending aortic dimension was referenced to the normative data (Fig. 6).[2] Based on this normative data, by the fifth week of life, the dimension of the ascending aorta had exceeded the expected mean.

A peripheral blood specimen was sent to the Laboratory for Molecular Medicine, Center for Genetics and Genomics, Harvard Medical School, Cambridge, MA, USA. After amplification using primer sets flanking each exon of the transforming growth factor (TGF) beta-receptor type II (TGFBR 2), the full TGFBR 2 gene sequencing of the polymerase chain reaction products was performed using an ABI fluorescence automatic DNA sequencer. DNA analysis revealed a previously-reported mutation, 1583G>A (R528H) in exon 7, of the TGFBR2 gene. This mutation is associated with LDS and is a more severe vascular disease. Two other variants were identified, a 263+7A>G variant that is common in the general population, and a 1167C>T (N389N) variant that is not expected to have clinical or pathological significance as it does not result in a change in the amino acid.

DISCUSSION

LDS is a recently-described syndrome, characterised by abnormal cardiovascular, craniofacial, neurocognitive

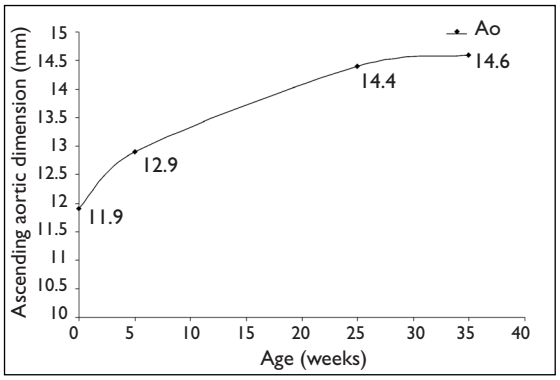

Fig. 5 Graph shows the dilatation of the ascending aorta with time.

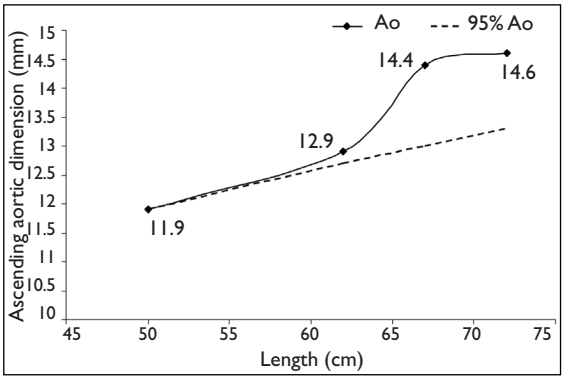

Fig. 6 Graph shows the dilatation of the ascending aorta with respect to length.

and skeletal development. It was first described in 16 individuals from ten families in 2005, and demonstrates autosomal dominant inheritance.[3] It has been described in Caucasian, Japanese[4] and Korean[5] individuals. The phenotypic features of individuals with LDS overlap with other genetic connective tissue disorders like MFS. However, there are characteristic phenotypic features that point to a clinical diagnosis of LDS, which has been described as being characterised by a triad of arterial tortuosity and aneurysms, hypertelorism and bifid uvula or cleft palate. In an early paper, Loeys et al cateogorised patients as Type I if the craniofacial involvement consisted of cleft palate, hypertelorism and craniosynostosis; and Type II if they had none of these abnormalities but an isolated bifid uvula.[3] In general, individuals with more severe craniofacial abnormalities tend to develop more severe and aggressive arterial disease. Given the significant craniofacial features of our patient, she would be classified as a Type I LDS, and utilising the craniofacial severity index for LDS patients,[3] she would have a score of 5. In the 2005 paper by Loeys et al, Type I patients had a mean score of 4.8 (range 0–11). The higher the score, the more severe the craniofacial abnormality.[1] Therefore, our patient's arterial disease is more likely to take a malignant course. A magnetic resonance (MR) angiogram from the head to the pelvis had been planned in our patient to look for aneurysms in other parts of the arterial tree and associated hydrocephalus and Chiari Type 1 malformation. The key clinical features of LDS Type I are listed in Table I. The physical findings in patients with LDS Type II include vascular rupture during pregnancy, and splenic and bowel rupture.

The prevalence of this genetic syndrome has not yet been established. LDS may be more common than expected and could be commonly misdiagnosed as MFS, Beals syndrome, Ehlers-Danlos syndrome, Larsen syndrome or "arthrogryposis complexes". Interestingly, patients thought previously to be Ehlers-Danlos syndrome Type IV, but with no mutation detected in the COL 3A1 gene, were tested positive for mutations in genes,[6] and reclassified as LDS. The TGF-beta signalling pathway comprises a large family of cytokines that bind to a Type 1 receptor, a serine-threonine receptor kinase, which then phosphorylates a Type 2 receptor, with a subsequent activation of transcription factors. The pathway is integral to many basic cellular processes, including cell differentiation, embryogenesis and apoptosis. This signalling pathway has been found to be defective in a range of syndromes such as MFS,[7] Sphrintzen-Goldberg syndrome[8] and LDS. In MFS, mutations in the fibrillin-1 gene result in decreased expression, altered stability or altered structure of the fibrillin-1 protein. A decrease in the amount of functional fibrillin-1 protein then results in over-activation of the TGF-beta signalling pathway with subsequent signs and symptoms of MFS. In LDS, the abnormality is more distal in the TGF-beta signalling pathway, with probands having mutations in either the TGFBR1 or TGFBR2. In the 42 probands described by Loeys et al, 29 (69%) had mutations in TGFBR2 and 13 (31%) had mutations were in TGFBR1.[3] This genotype is associated with histological evidence of elastin disarray, loss of elastic fibre architecture and increased collagen expression in the aortic media of patients, translating into the phenotype of LDS. The analysis for mutations in the TGFBR1 or TGFBR2 gene is currently being offered on a clinical basis at a few overseas laboratories.

The key feature of cardiovascular involvement in LDS is the marked arterial tortuosity, aortic root dilatation, and dissection of the aorta and its branches. It is important to emphasise that, unlike MFS, in which the arteriopathy seems to be confined to the ascending aorta, in LDS, aneurysmal dilatation of the abdominal aorta, pelvic vessels and intracranial vessels can occur, in addition to aortic involvement. Also, in LDS, the arterial dilatation and tortuousity tend to occur earlier and progress more rapidly, and the aortic root dissections

Table I. Clinical features of the Loeys-Dietz syndrome Type I.[1]

Characteristic	Loeys et al's study[3]	Current study
Cardiovascular		
Aortic root aneurysm	98%	+
Arterial tortuosity	84%	N.S.
Aneurysms of other vessels	52%	N.S.
Patent ductus arteriosus	35%	+
Atrial septal defect	22%	+
Craniofacial		
Hypertelorism	90%	+
Cleft palate / bifid uvula	90%	+
Craniosynostosis	48%	−
Malar hypoplasia	60%	−
Retrognathia	50%	+
Blue sclera	40%	+
Skeletal		
Arachnodactyly	70%	+
Pectus deformity	68%	+
Scoliosis	50%	−
Joint laxity	68%	+
Dolichosternomelia	18%	+
Talipes equinovarus	45%	−
Camptodactyly	38%	+
Cervical spine instability	18%	N.S.
Neurocognitive		
Hydrocephalus	15%	−
Chiari I malformation	10%	−
Developmental delay	15%	+

+: present; −: absent; N.S.: not seen in the patient

occur at smaller aortic root dimensions compared to patients with diagnosed MFS. Dilated aortas have been described in LDS patients antenatally.[9]

In their surgical cohort of 14 paediatric patients with a mean age of 9.2 (range 0.5–17) years, Williams et al performed surgery for aortic root aneurysms, with the aortic root dimension ranging 2.74–5.2 cm. There were no perioperative deaths. Although they noted that their series was small and had a short follow-up period, they recommended aortic root replacement in adult patients with aortic root dimension of 4 cm, and earlier in children with progressive aortic root dilatation and who have an aortic annulus of sufficient size to accept a graft that can accommodate growth (usually ≥ 2 cm). Up to two-thirds of patients with LDS had aneurysmal disease extending beyond the ascending aorta with sites including the thoracic aorta, abdominal aorta, pulmonary artery, coronary, vertebral, carotid, splenic, superior mesenteric and inferior mesenteric vessels.[10] These, like aneurysms of the ascending aorta, are also at risk of rupture and dissection. In Loeys' cohort, the mean age of death was 26 years and the median survival was 37 years. The leading cause of death was dissection of the thoracic aorta (67%), followed by dissection of the abdominal aorta (22%) and dissection involving the cerebral vasculature (7%).[3] Because of this risk, Williams et al recommended that patients with LDS have echocardiograms every three months and an annual computed tomography or MR angiography for surveillance of the whole arterial tree.[10]

Other major defects that the clinician should look for include cervical spine abnormalities, intracranial abnormalities and eye complications. In their series of five paediatric patients aged between one month and 9 years, Yetman et al noted that all had associated C2–C3 vertebral subluxation, and of these, two had evidence of spinal stenosis.[11] In view of the possible cervical spine instability, patients with LDS will require orthopaedic evaluation, and in particular, before general anaesthesia for cardiac surgery or MR imaging. There is an association with hydrocephalus and Chiari Type I abnormality, and a neurosurgical consult should be sought if these are present. Retinal haemorrhage and retinal detachment are eye complications associated with LDS. Lens dislocation is not strongly associated with this genetic disorder.

As alluded to earlier, the altered activity of the TGF-beta is common to both LDS and MFS. Losartan is an angiotensin-1 receptor antagonist, commonly used in the treatment of hypertension. Aggressive blood pressure control, to reduce haemodynamic vascular stress, is a key component in the management of patients with aortic aneurysms. In addition, losartan has been found to have a secondary effect in blocking TGF-beta activity – the pathway that has been found to be responsible for LDS. The studies on losartan have been conducted on the mouse model of MFS.[12] Losartan has been previously found to have anti-TGF-beta effects in animal models of cardiomyopathy[13] and chronic renal failure.[14] The mechanism by which angiotensin type 1 blockade antagonises TGF-beta signalling pathway remains to be fully studied; however, signalling through angiotensin type 1 receptor has been found to increase the expression of TGF-beta ligands and receptors. Matt et al showed that the mouse model of MFS was also associated with increased TGF-beta signalling. This increased activity can be prevented by the TGF-beta neutralising antibody and also by losartan. In their study, losartan-treated MFS mice appeared to have a full correction of the phenotypic abnormalities in the aorta wall, as compared to propanolol, which only seemed to slow the rate of aortic root growth.[15] Clinical trials are currently underway to study the effect of losartan in human subjects with MFS. The effect of losartan on patients with LDS is currently unknown, but given that both MFS and LDS individuals have defective TGF-beta signalling and that excessive TGF-beta signalling has been demonstrated in the aortic wall of individuals with LDS, therapy with losartan may

also be of clinical relevance in individuals with LDS. Based on our present understanding of the pathways involved in LDS and with the aggressive nature of the vascular lesions, it should be strongly considered in patients with genetically-confirmed LDS, particularly those in whom there is evidence of progression of the arteriopathy. We will be starting our patient on losartan, beginning at a dose of 0.7 mg/kg/day, building up to a dose of 1.4 mg/kg/day if tolerated.

In view of the aggressive nature of the associated arteriopathy, it is important that physicians identify patients with possible LDS, and distinguish LDS from MFS and other genetic disorders of connective tissues. This syndrome should be clinically suspected in patients with typical craniofacial abnormalities and early, rapid dilatation of the aortic root on 2D echocardiography. Given the recent recognition of LDS, the natural history of this disorder remains to be further studied. However, from current experience, patients with LDS will require close monitoring and follow-up, as early surgery may be needed before dissection or rupture of blood vessels occur. Losartan is a promising therapy that lowers blood pressure, thereby reducing haemodynamic stress on vascular walls; and it also acts by direct antagonism of the TGF-beta activity – the pathway found to be responsible in LDS. Losartan is currently being studied in the treatment of aortic dilatation associated with MFS, a disorder also associated with an abnormal TGF-beta pathway, and should be further studied in the management of patients with LDS.

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