



# Surgical treatment of Loeys-Dietz syndrome in a 3-year-old: case report and review of literature

Miao Tian<sup>1,2</sup>, Ming-Sing Si<sup>3</sup>, Yong Zhang<sup>2</sup>, Yu Ding<sup>2</sup>, Jimei Chen<sup>2</sup>

<sup>1</sup>Department of Cardiac Surgery, Guangdong Provincial People's Hospital, School of Medicine, South China University of Technology, Guangzhou, China; <sup>2</sup>Department of Cardiac Surgery, Guangdong Provincial Cardiovascular Institute, Guangdong Provincial Key Laboratory of South China Structural Heart Disease, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China; <sup>3</sup>Department of Cardiac Surgery, Section of Pediatric Cardiovascular Surgery, University of Michigan, Ann Arbor, MI, USA

*Correspondence to:* Jimei Chen. Department of Cardiac Surgery, Guangdong Provincial Cardiovascular Institute, Guangdong Provincial Key Laboratory of South China Structural Heart Disease, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China. Email: [jimei@hotmail.com](mailto:jimei@hotmail.com).

**Abstract:** Aortic complications of Loeys-Dietz syndrome (LDS) rarely present in children. Here we describe a case of LDS type 2 in a 3-year-old child with severe aortic root dilation and severe aortic regurgitation. A Bentall procedure combined with a Cabrol-type coronary modification was used to treat this child. In order to minimize the need for reintervention as the child grows. We chose a composite valve-graft by a St Jude Regent 21# mechanical valve seated within a 24 mm Gore-Tex graft to finish the Bentall procedure. Echocardiographic studies demonstrated good valve and ventricular function at 1-year follow-up. This child is one of the youngest LDS patients to receive a Bentall procedure and the way using a composite valve-graft to finish the operation can provide a reference for the surgical strategies of such patients in the future. Children with LDS and severe aortic annulus dilatation combined with severe aortic valve regurgitation require early surgical intervention, and implantation of a mechanical valved-conduit can be utilized successfully. Life-long follow-up of the valved-conduit and arterial vessels of these patients is necessary. The experience gained from this case contributes to the management of the rare LDS patient who presents at an early age with aortic root and valve pathology. Close monitoring and early intervention are important.

**Keywords:** Loeys-Dietz syndrome (LDS); surgery; autosomal dominant inheritance; gene mutation; case report

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## Introduction

Loeys-Dietz syndrome (LDS) is an autosomal dominant disorder of the connective tissue that was described in 2005 (1). Patients with mutations in the *TGFBR1*, *TGFBR2*, *TGFB2*, *TGFB3*, and *SMAD3* genes were noted to present with phenotypical features of LDS. LDS affects tissues and organs throughout the body, especially the great arteries. Rapidly progressive aortic aneurysmal disease is a distinct feature of LDS and thus mandates close monitoring of these patients. Early prophylactic surgery is crucial to avoid catastrophic aortic complications and achieve a good long-term prognosis (2). Here we present a case of a young child

with LDS who was implanted a composite valve-graft by a St Jude Regent 21# mechanical valve seated within a 24 mm Gore-Tex graft to finish the Bentall procedure and achieved a favourable post-operative follow-up outcome, describe the presenting signs and symptoms, and discuss the clinical management. We present the following case in accordance with the CARE reporting checklist (3) (available at <http://dx.doi.org/10.21037/tp-20-146>).

## Case presentation

Written informed consent was obtained from the patient's parents. All procedures performed in studies involving

**Table 1** Transthoracic echocardiogram (TTE) results of the aortic annulus, aortic sinus, sinotubular junction and ascending aorta at different age

	Aortic annulus (mm)	Aortic Sinus (mm)	Sinotubular junction (mm)	Ascending aorta (mm)	Aortic valve regurgitation (cm <sup>2</sup> )	LVEF (%)
22 months	23	29	17.6	13.9	4.3	77
24 months	22	29	–	16	5.6	80
30 months	21.6	29.4	–	18.2	4.3	64
35 months	23.7	30	–	16	3.4	62
38 months	23	33	17	18.6	4.3	68



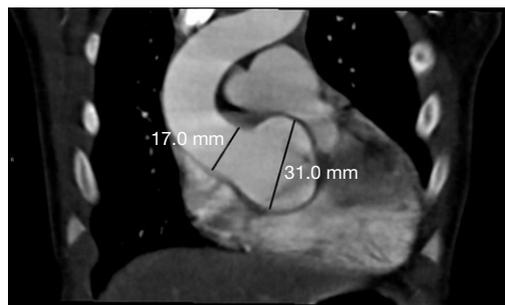
**Figure 1** Pediatric LDS patient with middle finger spasm bilaterally, inguinal hernia, and hyperextension of the knees. LDS, loeys-Dietz syndrome.

human participants were in accordance with the ethical standards of the Guangdong Provincial People's Hospital ethical review committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents for publication of this Case report and any accompanying images. A three-and-half year-old-boy with a history of LDS was referred for surgical intervention after a transthoracic echocardiogram (TTE)

demonstrated a dilated aortic annulus (diameter: 23 mm, z score 11.59) and ascending aorta (diameter:18.6 mm, z score 3.99) as well as severe regurgitation and left ventricle dilation and decreasing systolic function (*Table 1*). Notably, on physical examination, he was noted to have middle finger spasm bilaterally, inguinal hernia, and hyperextensibility of the knees (*Figure 1*). At 7 months of age, an echocardiogram demonstrated left ventricular enlargement, a patent

**Table 2** Gene sequencing indicated a heterozygous missense mutation of the *TGFBR2* gene: 1634G-->T, leading to an amino acid change of C545F

Gene	Chromosome location	Transcript number	Exon	Nucleotide change	Amino acid change	Homozygous/heterozygous	Normal frequency	Pathogenicity analysis	Genetic way	Disease/phenotype	Sources of variation
<i>TGFBR2</i>	Chr3-30732946	NM_001024847	Exon8	c.1634G>T	p.C545F	het	–	Likely pathogenic	AD	LDS (type 2)	Spontaneous mutation

**Figure 2** CT scan at 2 years of age demonstrated a dilated aortic annulus and ascending aorta.

foramen ovale, aortic sinus dilatation (diameter: 24 mm), ascending aortic dilation (diameter: 14 mm), and moderate regurgitation of aortic valve (regurgitation area: 1.5 cm<sup>2</sup>). Based on these echocardiogram findings, gene sequencing was performed at that time and revealed a heterozygous missense mutation of the *TGFBR2* gene: 1634G-->T, leading to an amino acid change of C545F (Table 2). Parental gene sequencing did not reveal any abnormalities. Given the physical signs, echocardiogram findings, and genomic studies, a diagnosis of LDS type 2 (OMIM: 610168) was made.

The child's aortic regurgitation was monitored closely, and serial TTE over the first three years of life demonstrated progressive dilation of the aortic annulus, aortic sinus, sinotubular junction, and ascending aorta (Table 1). Further, aortic regurgitation progressively worsened (Table 1). A CT of the head and neck demonstrated an enlarged skull and no obvious dilation or deformity of the head and neck blood vessels. A CT at 2 years of age demonstrated a dilated aortic annulus and ascending aorta (Figure 2).

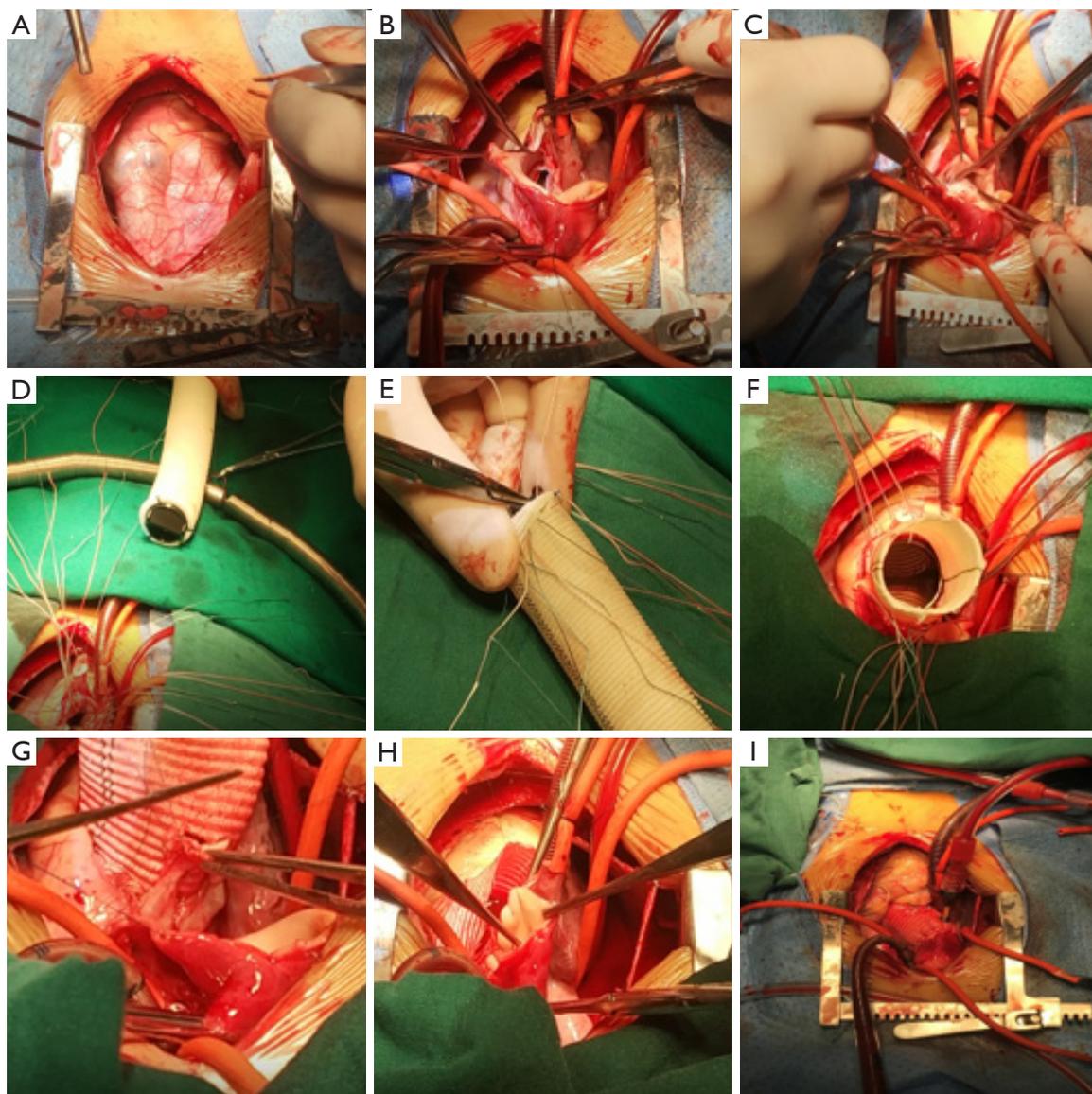
Because of the severe aortic valve regurgitation resulting in rapid and progressive left ventricle dilation, the patient underwent a Bentall procedure at 3 years and 3 months of age. His extremely dilated aortic annulus was felt to be a contraindication to a valve sparing aortic root replacement procedure. After coronary buttons were harvested and diseased sinus tissue resected (Figure 3A,B,C), a composite valve-graft by a St Jude

Regent 21# mechanical valve seated within a 24 mm Gore-Tex graft was implanted (Figure 3D,E,F). Given the distance between the coronary buttons and the aortic graft, Cabrol extension of the coronary arteries was performed (Figure 3G,H,I). Postoperative transesophageal and transthoracic echocardiography demonstrated good aortic valve function with no perivalvular regurgitation and laminar coronary flow. The cardiopulmonary bypass time was 193 min and the aortic cross clamp time was 121 min. Pathological examination revealed that the aortic valve had undergone degeneration with interstitial fibrous hyperplasia, focal collagenization, myxoid degeneration and focal calcification (Figure 4A). Furthermore, the resected aneurysmal aorta revealed a thin wall with inflammatory infiltrate (Figure 4B). The patient had an uneventful postoperative recovery and was discharged on postoperative day 12 with losartan and warfarin. The timeline of this case was shown in Figure 5.

At 3 months follow-up, TTE demonstrated normal left ventricle function, a functioning prosthetic aortic valve and mild tricuspid regurgitation. The proximal part of the ascending aorta diameter was 21.2 mm and a mild gradient was measured in the proximal aortic arch (Vmax 1.6 m/s). At 1-year post repair, the patient continued to do well with improved tricuspid regurgitation, stable aortic dimensions, a functioning prosthetic aortic valve and normal left ventricle function.

## Discussion

LDS was originally described in 16 individuals from ten families (4). Patients with LDS exhibit a variety of features, mainly involving the cardiovascular, musculoskeletal and central nervous systems (5). *TGFBR1* and *TGFBR2* mutations were initially shown to cause LDS, with subsequent pathogenic mutations identified in *SMAD3*, *TGFB2*, and *TGFB3*. Pathogenic mutations in all of these genes, which encode mediators of the TGF signaling pathway, result in loss of function of the protein product (6), causing elastin disarray, loss of elastic fiber architecture and increased collagen expression in the aortic media of

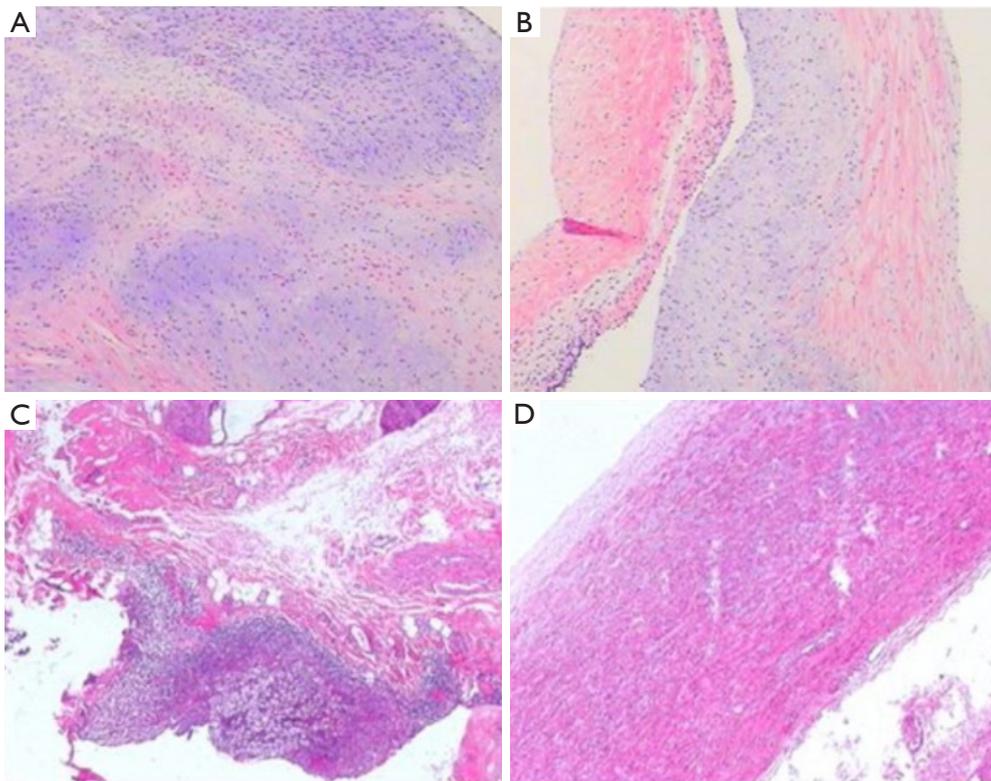


**Figure 3** Bentall procedure performed with a composite valve-graft comprised of a St Jude Regent 21# mechanical valve within a 24 mm Gore-Tex graft. (A) A dilated aortic annulus (diameter: 30 mm) and ascending aorta. (B) The aortic valve and aneurysmal aorta were excised. (C) Harvesting of coronary buttons. (D,E,F) A composite valve-graft was created with a St Jude Regent 21# mechanical valve in a 24 mm Gore-Tex graft was implanted. (G) Cabrol extension of the coronary arteries was performed. (H and I) The Gore-Tex graft was anastomosed to the ascending aorta.

patients. The aortic wall is characterized by medial diffuse degeneration and elastin fragmentation (7). Because of these structural changes, the vascular media weakens and makes the aorta prone to aneurysmal dilation and dissection (4,5,8).

Half of LDS patients with severe craniofacial features are at particularly high risk, known to have aneurysm rupture at an early age and at smaller dimensions than those with

other aneurysm syndromes (1,4). It has been reported that patients with LDS undergo cardiovascular operations earlier (mean age, 16.9 years) and die earlier (mean age, 22.6 years) but have a lower intraoperative mortality rate (9). The reported median age at first dissection for patients with LDS is 26.7 years (10) and the mean age of death was 26 years and the median survival was 37 years. The leading



**Figure 4** Pathological examination of the aortic valve. (A,B) Degenerative changes with interstitial fibrous hyperplasia, focal collagenization, myxoid degeneration and focal calcification (magnification 40 $\times$ ). (C,D) Inflammatory infiltrate was also present in the resected aneurysmal aorta (magnification 40 $\times$ ).

cause of death for LDS was dissection of the thoracic aorta (67%), abdominal aorta (22%), and the cerebral vasculature (7%) (4). The vascular phenotype of LDS, characterized by aneurysmal changes and tortuosity of the arteries, is not limited to the aortic root, and lifelong serial imaging of the entire arterial tree, both systemic and pulmonary, is mandatory (11).

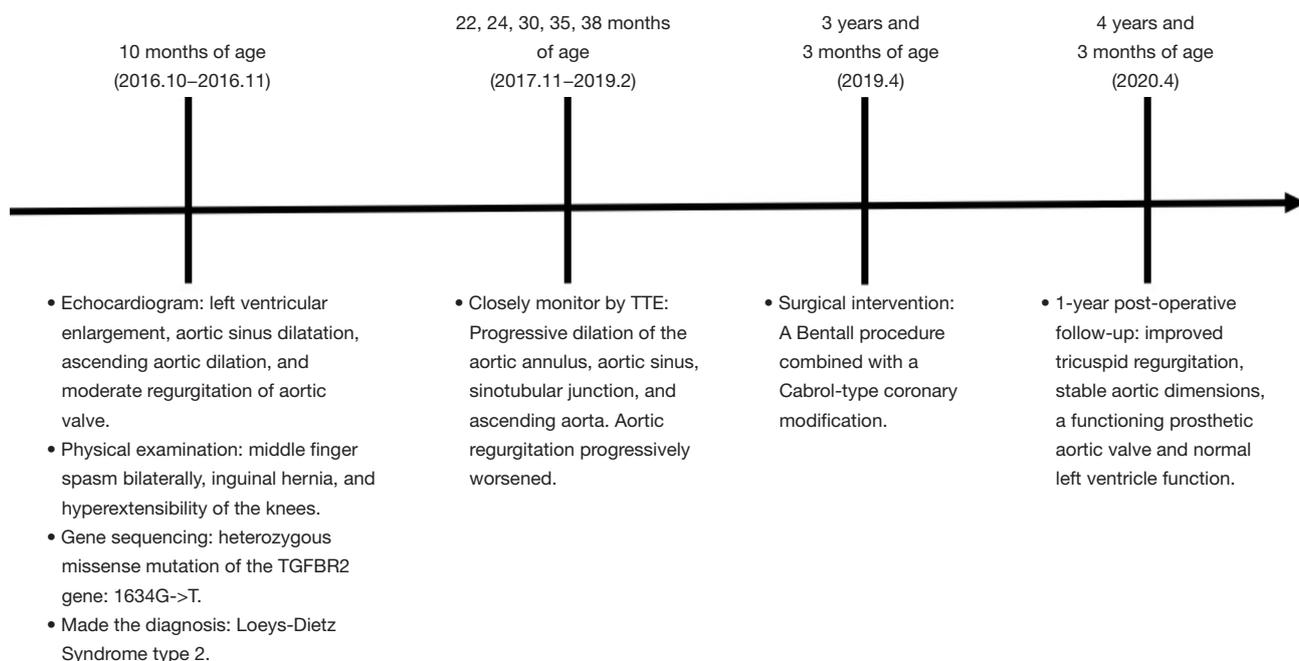
The decision to undergo aortic surgery is typically based on the absolute dimension of the aorta, rate of progression, aortic valve function, severity of noncardiac features, family history, and information about genotype (4,12). A clinical study including 53 LDS patients, 33 of whom underwent aortic surgery noted that close monitoring and early prophylactic interventions were the key to avoid aortic catastrophe and to achieve a good long-term prognosis (2).

This child is one of the youngest LDS patients to receive a Bentall procedure. Progressive aortic dilation and severe aortic valve insufficiency mandated early intervention. Fortunately for this patient, we were able to implant an

adult-sized valved conduit. However, the consequence of this operation is that this child will need life-long anticoagulation.

Early genetic testing is warranted if the physical examination and history are suggestive of LDS. Further, genetic testing will permit the differentiation of these patients from those with Marfan syndrome. Close follow up is required for children with LDS, provided there is no life-threatening dissection or aneurysm in the aorta and the function of the aortic valve is not significantly impaired.

Children with LDS and aortic dilation and aortic valve regurgitation should be closely followed. Treatment with a Bentall procedure or valve sparing root replacement are required and adult-sized grafts and valves will minimize the need for reintervention as the child grows. Continued life-long follow-up in these patients is needed to monitor the rest of the arterial tree, which is susceptible to aneurysmal dilation and complications and may require prophylactic intervention.



**Figure 5** The timeline of this case.

The limitation of this study is that this patient should need life-long anticoagulation and we can't predict whether and when other arteries need intervention. We need the long-term follow-up consequence to evaluate our surgical strategies.

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## Footnote

**Reporting Checklist:** The authors have completed the CARE reporting checklist. Available at <http://dx.doi.org/10.21037/tp-20-146>

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tp-20-146>). MSS serves as an unpaid Deputy Editors-in-Chief of *Translational Pediatrics* from Dec 2018 to Nov 2020. The other authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Guangdong Provincial People's Hospital ethical review committee and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient's parents for publication of this Case report and any accompanying images.

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