HK J Paediatr (new series) 2012;**17**:248-253

Case Reports

Two Chinese Patients with Loeys-Dietz Syndrome: A Connective Tissue Disorder with Marfan-like Features and Vasculopathy

ACC ***Ho,*** SY ***Chan,*** PC ***Chow,*** KT ***Wong,***
KS ***Lun,*** IFM ***Lo,*** STS ***Lam,*** KT ***Chau,*** YL ***Lau,*** BHY ***Chung***

Abstract Loeys-Dietz syndrome (LDS) is an autosomal dominant connective tissue disorder characterised by unique facial dysmorphology and aggressive vasculopathy. It is caused by mutations in genes encoding transforming growth factor beta receptor Type 1 or Type 2 (*TGFBR1* and *TGFBR2*). There is substantial phenotypic overlap with other connective tissue disorders, especially Marfan syndrome. We present 2 patients whom we previously reported to have Marfan-like phenotype. They were reassessed clinically and molecularly and confirmed to have Loeys-Dietz syndrome. It is of vital importance for paediatricians to recognise this recently described connective tissue disorder in order to provide appropriate surveillance and early intervention to improve the prognosis.

Key words Connective tissue disorder; Loeys-Dietz syndrome; Marfan syndrome; Transforming growth factor beta receptor

Department of Paediatrics and Adolescent Medicine, Queen Mary Hospital, Li Ka Shing Faculty of Medicine, The University of Hong Kong, 102 Pokfulam Road, Pokfulam, Hong Kong, China

ACC **Ho** (何智聰) *MBBS, MRCPCH*
SY **Chan** (陳樹仁) *MRCPCH, FHKAM(Paed)*
PC **Chow** (周百昌) *MBBS, MRCP(UK), FHKAM(Paed)*
KT **Wong** (黃健德) *MBBS, MRCP(UK), FHKAM(Paed)*
KS **Lun** (倫建成) *FRCP(Edin), FHKAM(Paed), FHKCPaed*
KT **Chau** (周啟東) *FRCPCH, FHKAM(Paed), FHKCPaed*
YL **Lau** (劉宇隆) *MD*
BHY **Chung** (鍾侃言) *MBBS(Hons), FHKAM(Paed), FCCMG(Clinical Genetics)*

Clinical Genetic Service, Department of Health, Hong Kong, China

IFM **Lo** (盧輝文) *FHKAM(Paed), FHKCPaed*
STS **Lam** (林德深) *MD, FRCP*

Correspondence to: Dr BHY **Chung**

Received January 20, 2012

Introduction

Loeys-Dietz syndrome (LDS, OMIM 609192) is a recently described autosomal dominant disorder of connective tissue first reported in 2005.[1] It is caused by heterozygous mutations in the genes encoding transforming growth factor beta receptor 1 or 2 (*TGFBR1* or *TGFBR2*). LDS has a phenotypic overlap with other connective tissue disorders, especially Marfan syndrome. It is important to differentiate between LDS and Marfan syndrome as the former is characterised by generalised arterial tortuosity and aortic dissections or ruptures at smaller diameters.

Here, we present two Chinese patients with LDS. They were two of the six patients we reported to have Marfan-like features and *TGFBR2* mutations in 2009.[2] Childhood and adolescence photographs were obtained with permission to demonstrate the evolution of clinical features in LDS patients.

Case Report

Patient A

Index Patient A was born full term with birth weight of 3.6 kg. He was the first child of a non-consanguineous Chinese couple. From history, he was diagnosed to have 'hydrocephalus' at 6 months old and was managed conservatively. He underwent surgical repair of bilateral inguinal hernia during infancy. He was referred for assessment of heart murmur at 8 years old. Physical examination showed hypertelorism (latest inter-pupillary distance of 7.3 cm at 17 years old), submucosal cleft palate, joint hyperlaxity, arachnodactyly, thumb sign and wrist sign (Figure 1). Echocardiogram performed at 8 years old demonstrated patent foramen ovale, patent ductus arteriosus, dilated aortic root (the aortic sinus was measured to be 4.7 cm equivalent to z-score for body surface area of +7.03) and mild to moderate aortic regurgitation. Ophthalmological assessment was normal. Atlanto-axial subluxation was confirmed by cervical X-ray while

Figure 1 Clinical photographs of Patient A and Patient B. Both Patient A and Patient B have a typical 'Marfanoid habitus' and facial features including facial asymmetry, malar hypoplasia and hypertelorism. Patient A has submucosal cleft palate, while Patient B has bifid uvula. Arachnodactyly is present in both, but thumb sign and wrist sign are only positive in Patient A, while they are absent in Patient B, who had a surgery for camptodactyly at 7 years old. Evolution of clinical features can be appreciated from the childhood photographs provided by the patients.

lumbosacral spine was normal.

He was managed as Marfan syndrome. Pre-operative cardiac catheterisation at 9 years old confirmed aortic root dilation, while the aortic arch was not dilated. Aortic root replacement, together with direct suture of patent foramen ovale and ligation of patent ductus arteriosus, were performed. Serial CT aortograms revealed progressive dilation of aortic arch distal to the aortic valve conduit. At the age of 16, the aortic arch at the level of right pulmonary artery was measured to be 8.3 cm corresponding to a z-score for body surface area of +8.98. A second operation, aortic arch replacement, was performed at the same year.

Subsequent genetic study revealed a c.973A>C/p.T325P missense mutation in the *TGFBR2* gene (Figure 2). Fibrillin-1 (*FBN1*) gene testing was negative.

Patient B

Index Patient B was born full term with birth weight of 2.7 kg. He was the first child of a non-consanguineous Chinese couple. He had dysmorphic features including abnormal head shape, hypertelorism (latest inter-pupillary distance of 7 cm at 16 years old), bifid uvula, malar hypoplasia, arachnodactyly, left divergent squint and pectus excavatum. Thumb sign and wrist sign were negative (Figure 1). He developed significant camptodactyly and required right hand reconstruction of the ulnar drifting at 7 years old. Echocardiography performed at 8 years old demonstrated dilated aortic root (the aortic sinus was measured to be 3.5 cm corresponding to a z-score for body surface area of +4.59). Pectus excavatum was progressive and required surgical repair in terms of metal rod insertion at 11 years old. He was managed as non-specific connective tissue disease and was put on metoprolol for his dilated aortic root. However, aortic root dilation was progressive. By age 13, it was measured to be 4.8 cm (z-score: +6.66). Aortic root replacement was performed at the same year. Scoliosis was prominent with Cobb's angle measuring 29 degrees from T4 to T10 and 22 degrees from T10 to L3 when he was 16 years old. Cervical X-ray also showed left lateral flexion deformity.

Subsequent genetic study revealed a c.1069G>A/p.G357R missense mutation in *TGFBR2* gene (Figure 2) while *FBN1* gene testing was negative.

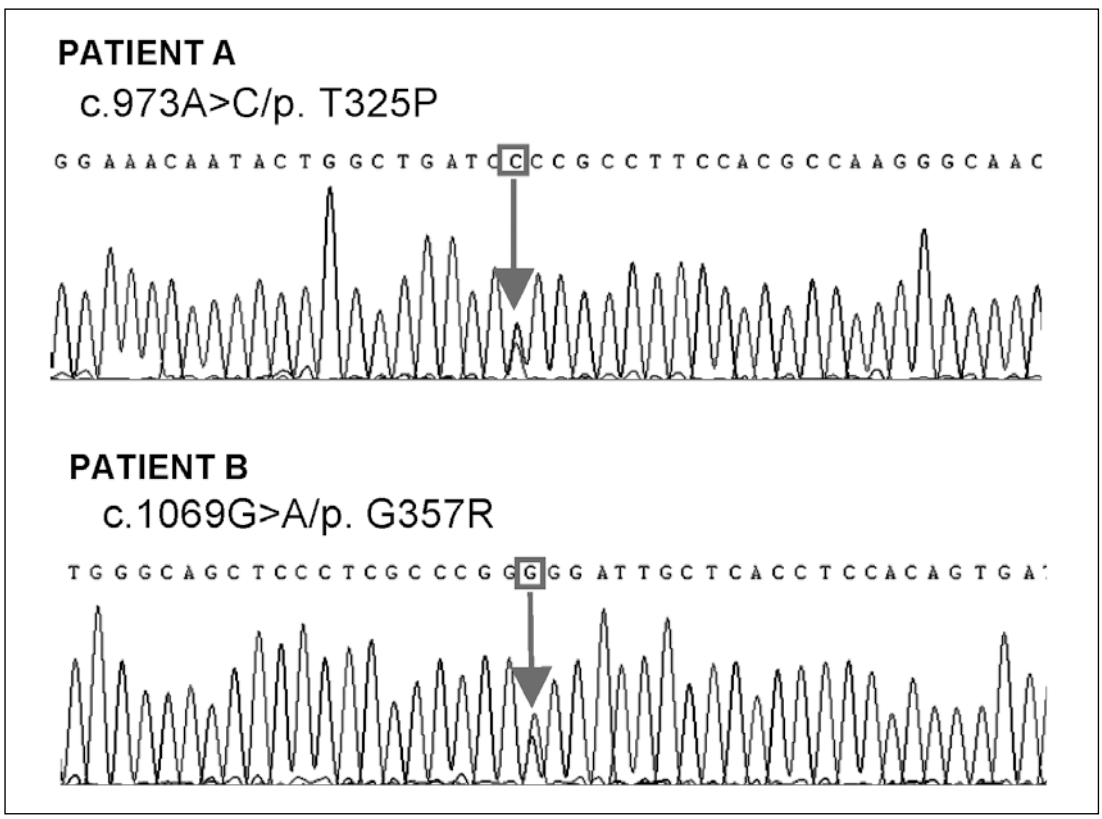

Figure 2 Chromatogram showing mutations c.973A>C/p.T325P and c.1069G>A/p.G357R in TGFBR2 gene in Patient A and B.

Discussion

LDS is characterised by the triad of hypertelorism, cleft palate or bifid uvula and arterial tortosity. Symptoms can start to appear in the neonatal period.[3,4] As LDS is a relatively new clinical condition and many of the LDS patients might be misdiagnosed as Marfan syndrome, data concerning the epidemiology of LDS is not available. It can be classified into 2 types.[5] About 75% of patients belong to Type 1, which present with craniofacial abnormalities including hypertelorism, cleft palate/bifid uvula, craniosynostosis (premature closure of cranial sutures), malar hypoplasia, retrognathia and blue sclera. Ectopia lentis, one of the diagnostic criteria of Marfan syndrome, is typically absent in LDS patients.[5-7] Both of our patients had significant craniofacial abnormalities and should belong to LDS Type 1. Hypertelorism is typically measured by inter-pupillary distance. Although standard percentile chart of inter-pupillary distance specific for Chinese is not available, the hypertelorism in our two patients is considered obvious from inspection and both are above 97th percentile by Caucasian's standard.[8]

The remaining 25% of patients belong to Type 2, in which craniofacial abnormality (besides isolated bifid uvula) is typically absent. Instead, Type 2 LDS patients share clinical features with vascular Ehlers-Danlos syndrome which consist of vascular rupture during pregnancy, visceral organ rupture, marked joint laxity and cutaneous manifestations including easy bruising, atrophic scar and velvety translucent skin. Therefore, patients with vascular Ehlers-Danlos syndrome phenotype, but with normal biochemical analysis of Type III collagen and negative *COL3A1* gene mutation should be evaluated for LDS.[6]

In Marfan syndrome, *FBN1* mutation leads to decreased amount of functional fibrillin-1 protein, which results in over-activation of the TGF-beta signaling pathway and therefore symptoms and signs of Marfan syndrome. On the other hand, one-third and two-thirds of LDS is due to mutation of *TGFBR1* and *TGFBR2* respectively.[6] Subsequent increase in TGF-beta signaling and elastin disarray contributes to the features of LDS. According to Loeys' study, there is no difference in terms of clinical presentation between patients with *TGFBR1* and *TGFBR2* mutations.[5] In addition, LDS Type 1 and Type 2 can be resulted from mutations in either *TGFBR1* or *TGFBR2* genes.[6]

In the past, our patients were managed as Marfan syndrome and non-specific connective tissue disorder respectively. They were subsequently re-assessed and confirmed both clinically and molecularly to have LDS. Although there are substantial overlap of phenotypic features in LDS, Marfan syndrome and other connective tissue diseases, it is vital to differentiate them as the management and prognosis are different. Loeys et al developed a craniofacial severity index for LDS patients. The score can range from 0 to 11. Components of the score include hypertelorism, craniosynostosis and cleft palate / bifid uvula. A LDS patient is given a score of 2 for marked hypertelorism, 1 for subtle hypertelorism and 0 for no hypertelorism. He or she is going to receive a score of 6 if both craniosynostosis and cleft palate are present, and a score of 3 if either one is present. For malformation of uvula, a bifid uvula is given a score of 3, midline raphe a score of 2, a broad uvula with no cleft a score of 1 and a normal uvula a score of 0.[5] LDS Type 1 patients had a mean score of 4.8, while LDS Type 2 patients had a mean score of 0.8 (Range: 0-11).[5] The higher the score, the younger the age at the first cardiovascular event would be. Both of our patients scored 5 out of 11 (For Patient A, he scores 2 points from marked hypertelorism and 3 points from cleft palate. For patient B, he scores 2 points from marked hypertelorism and 3 points from bifid uvula.) and both of them had their first cardiovascular operation performed at the age younger than the mean age of first surgery in LDS Type 1 patients (16.9 years).[5]

Vasculopathy is a common feature of LDS and Marfan syndrome. However, it is important to realise that vascular disease is more aggressive and widespread in LDS than in Marfan syndrome. In contrast to vascular dilation in Marfan syndrome which is limited to aortic root, vasculopathy in LDS can also occur elsewhere. About twenty percent of LDS patients had aneurysms in the arteries of head and neck or in abdominal arterial branches.[5] As these regions cannot be adequately assessed by echocardiogram, CT angiogram or MR angiogram from head to pelvis is recommended for complete examination of the potentially affected arterial system. Furthermore, when compared with Marfan syndrome, rupture of aneurysms tends to occur earlier and at smaller sizes in LDS. In order to avoid aneurysm rupture, the threshold of aortic root surgery in LDS is lower than that in Marfan syndrome.

Apart from vasculopathy, skeletal features in LDS are also prominent and show considerable overlap with those of Marfan syndrome. Both diseases demonstrate arachnodactyly, joint hyperlaxity, pectus excavatum or pectus carinatum and scoliosis. Cervical spine instability, talipes equinovarus (contractures of feet) and

camptodactyly (contractures of fingers) are more commonly seen in LDS. On the other hand, dolichostenomelia (long limbs leading to increased arm span-to-height ratio) is less described in LDS.[6,9] Compared with *FBN1* gene mutation, skeletal involvement associated with *TGFBR2* mutation is usually less severe.[10] However, it is important to rule out cervical spine instability if surgery is anticipated. A comparison between the two connective tissue disorders is summarised in Table 1.

According to Loeys' study which included 90 LDS patients, the median survival was 37 years, which is lower than that in Marfan syndrome (70 years) and vascular Ehlers-Danlos syndrome (48 years).[5] The mean age of death was 26 years old. Thoracic aortic dissection (67%) is the leading cause of death, followed by abdominal aortic dissection (22%) and cerebral bleeding (7%).[5] There was no significant difference in terms of number of deaths between patients with LDS Type 1 and 2. However, the mean age of death tended to be lower in the LDS Type 1 group when compared with the LDS Type 2 group (22.6

Table 1 A comparison of phenotypic features between Marfan syndrome and Loeys-Dietz syndrome (LDS)

	Marfan syndrome	**Loeys-Dietz syndrome Type 1**	**Loeys-Dietz syndrome Type 2**
Involved Gene	*FBN1*	*TGFBR1 / TGFBR2*	*TGFBR1 / TGFBR2*
Cardiovascular system			
Aortic root aneurysm	Typical	Typical More aggressive when compared with LDS Type 2	Typical Less aggressive when compared with LDS Type 1
Aneurysm in sites other than aortic root	Rare	Common	Common
Arterial tortosity	Not associated	Typical	Typical
Bicuspid semilunar valves	Population risk	Common	Common
Atrial septal defect	Population risk	Common	Common
Patent ductus arteriosus	Population risk	Common	Common
Facial features			
Hypertelorism	Not associated	Typical	Not associated
Cleft palate/bifid uvula	Not associated	Typical	Occasional bifid uvula
Skeletal system			
Craniosynostosis	Not associated	Common	Not associated
Cervical instability	Not associated	Associated	Associated
Dolicostenomelia	Typical	Rare and subtle	Rare and subtle
Talipes equinovarus	Not associated	Associated	Observed
Ocular system			
Ectopia lentis	Typical	Not associated	Not associated
Skin			
Easy bruising	Not associated	Not associated	Typical
Wide and dystrophic scar	Not associated	Not associated	Typical
Skin translucency	Not associated	Observed	Typical
Central nervous system			
Dural ectasia	Common	Observed	Observed
Developmental delay	Population risk	Associated	Associated
Chiari I malformation	Not associated	Associated	Associated

years vs 31.8 years, p=0.06). The mean age of first surgery was also younger in LDS Type 1 group than in LDS Type 2 group (16.9 years vs 26.9 years, p=0.03).[5] Our patients who both belong to LDS Type 1 had aortic root replacement at 9 and 14 years respectively.

As Marfan syndrome, management of LDS should be focused on early detection and treatment of complications. Since vasculopathy is aggressive in LDS, the importance of regular assessment of cardiovascular status by echocardiogram and CT/MR angiograms cannot be over-emphasized. Beta blocker and angiotensin receptor blocker treatment may help to reduce hemodynamic stress and therefore further vascular dilation. Threshold of surgery is lower than that in Marfan syndrome and other connective tissue disorders. This is particularly true in those LDS patients with severe craniofacial features. According to Loeys et al,[5] surgery should be considered once the maximal diameter of the ascending aorta exceeds the 99th percentile in children or 4 cm in adolescents or adults.[5] In contrast, the threshold above which surgery is recommended in patients with Marfan syndrome is 5 cm.

Conclusion

LDS is a recently recognised connective tissue disorder which shares many phenotypic features with Marfan syndrome. It can be due to mutations in genes encoding transforming growth factor beta receptor Type 1 or Type 2 (*TGFBR1* or *TGFBR2*). It is of utmost importance for clinicians to recognise LDS as a differential diagnosis of Marfan-like phenotypes so that accurate genetic counseling, lifelong surveillance and timely surgical intervention can be offered, which can greatly improve the prognosis of patients with this disorder.

Acknowledgement

We would like to thank both patients and their families for providing us with the photographs for this report.

References

1. Loeys BL, Chen J, Neptune ER, et al. A syndrome of altered cardiovascular, craniofacial, neurocognitive and skeletal development caused by mutations in *TGFBR1* or *TGFBR2*. Nat Genet 2005;37:275-81.
2. Chung BHY, Lam STS, Tong TMF, et al. Identification of novel *FBN1* and *TGFBR2* mutations in 65 probands with Marfan syndrome or Marfan-like phenotypes. Am J Med Genet Part A 2009;149A:1452-9.
3. Yetman AT, Beroukhim RS, Ivy DD, Manchester D. Importance of the clinical recognition of Loeys-Dietz syndrome in the neonatal period. Pediatrics 2007;119:e1199-202.
4. Choo JT, Tan TH, Lai AH, Wong KY. Loeys-Dietz syndrome: a Marfan-like syndrome associated with aggressive vasculopathy. Singapore Med J 2009;50(10):e353-7.
5. Loeys BL, Schwarze U, Holm T, et al. Aneurysm syndromes caused by mutations in the TGF-beta receptor. N Engl J Med 2006;355:788-98.
6. Van Hemelrijk C, Renard M, Loeys B. The Loeys-Dietz syndrome: an update for the clinician. Curr Opin Cardiol 2010; 25:546-51.
7. Aalberts JJ, van den Berg MP, Bergman JE, et al. The many faces of aggressive aortic pathology: Loeys-Dietz syndrome. Neth Heart J 2008;16:299-304.
8. Hall JG, Allanson JE, Gripp KW, Slavotinek AM. Handbook of Physical Measurements, 2nd ed. New York: Oxford University Press, 2007.
9. Sousa SB, Lambot-Juhan K, Rio M, et al. Expanding the skeletal phenotype of Loeys-Dietz Syndrome. Am J Med Genet A 2011; 155A:1178-83.
10. Attias D, Stheneur C, Roy C, et al. Comparison of clinical presentations and outcomes between patients with *TGFBR2* and *FBN1* mutations in Marfan syndrome and related disorders. Circulation 2009;120:2541-9.