The many faces of aggressive aortic pathology: Loeys-Dietz syndrome

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Background: Loeys-Dietz syndrome (LDS) is a newly recognised disorder of connective tissue which shares overlapping features with Marfan syndrome (MFS) and the vascular type of Ehlers-Danlos syndrome, including aortic root dilatation and skin abnormalities. It is clinically classified into types 1 and 2. LDS type 1 can be recognised by craniofacial characteristics, e.g. hypertelorism, bifid uvula or cleft palate, whereas these are absent in LDS type 2. It is important to recognise LDS because its vascular pathology is aggressive. We describe nine LDS patients from four families, relate their features to published cases, and discuss important aspects of the diagnosis and management of LDS in order to make clinicians aware of this new syndrome.

Results: Characteristics found in the majority of these LDS patients were aortic root dilatation, cleft palate and/or a bifid/abnormal uvula.

Conclusion: Because aortic dissection and rupture in LDS tend to occur at a young age or at aortic root diameters not considered at risk in MFS, and because the vascular pathology can be seen throughout the entire arterial tree, patients should be carefully followed up and aggressive surgical treatment is mandatory. Clinicians must therefore be aware of LDS as a cause of aggressive aortic pathology and that its distinguishing features can sometimes be easily recognised. (*Neth Heart J* 2008;16:299-304.)

Keywords: Loeys-Dietz syndrome, connective tissue disorder, aortic pathology

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Aortic dissection and rupture can be associated with generalised connective tissue disorders, especially when these catastrophic events occur at a young age. The vascular type of Ehlers-Danlos syndrome (EDS) and Marfan syndrome (MFS) are the most prevalent connective tissue disorders in these patients.^{1,2} Recently, however, a newly recognised connective tissue disorder, Loeys-Dietz syndrome (LDS), has been described, which is also accompanied by these severe aortic complications.³ LDS is an autosomal dominantly inherited disorder of connective tissue caused by mutations in the transforming growth factor beta (TGF- β) receptor 1 or 2 genes.^{3,4} The exact prevalence is unknown but given the fact that LDS has only recently been discovered, many cases might not have been diagnosed yet. The first type of this syndrome (LDS type 1) has many overlapping features with Marfan syndrome (MFS), including aortic root dilatation, arachnodactyly (long slender fingers), dolichostenomelia (thin body habitus and long extremities), pectus deformity and joint laxity, whereas LDS type 2 has features that overlap with the vascular type of EDS (see table 1 for an overview of differentiating characteristics of the syndromes).^{3,4} Vascular pathology in LDS, however, is more aggressive than

Table 1. Major clinical features of Loeys-Dietz syndrome (LDS) type 1 and 2, Marfan syndrome and the vascular type of Ehlers-Danlos syndrome (EDS type IV).

	Marfan	LDS 1	LDS 2	EDS 4
Vascular				
Aortic aneurysm/dissection	++	+++	+++	+++
<i>Tortuosity</i>	-	+++	+++	-
<i>ASD</i>	-	+	+	-
Skeletal				
Arachnodactyly ^a	+++	++	++	-
Dolichostenomelia ^b	++	+		-
Pectus abnormalities	++	++	++	-
Joint laxity	++	++	+++	+ (Small joints)
<i>Pes equinovarus^c</i>	-	+		+
Facial				
Craniosynostosis ^d	-	+ / ++	-	-
<i>Hypertelorism^e</i>	-	+++	-	-
<i>Cleft palate/bifid uvula</i>	-	+++	+ (Uvula)	-
Skin				
Excessive striae	+	-	-	-
<i>Easy bruising</i>	-		+++	++
<i>Soft, velvety, translucent</i>	-	+	++ / +++	+++
Eyes				
<i>Ectopia lentis^f</i>	++	-	-	-
Other				
<i>Rupture large organs</i>	-	-	+ / ++	++

The presence or absence of the features in italics might help to differentiate from Marfan syndrome. -infrequently, + around 25-50%, ++ around 50-75%, +++ >75%.

^along slender fingers, ^bthin body habitus and long extremities, ^cclubfeet, ^dpremature closure of cranial sutures, ^eincreased distance between pupils, ^flens subluxation.

in MFS.³⁻⁵ It is therefore of uttermost importance to recognise this disorder. This is facilitated by distinctive, frequently occurring and easily recognisable characteristics of LDS (table 1).^{3,4}

In order to publicise these features, we describe nine patients, from four families, who presented to our department and in whom we genetically confirmed LDS. In addition, we discuss some important aspects concerning the diagnosis and management of LDS.

Patients and methods

Patients

All patients and families were referred to our Marfan outpatients' clinic to evaluate a possible diagnosis of MFS or other connective tissue disorder. Subjects were characterised both clinically and genetically, and the diagnosis of LDS was confirmed by a mutation in the TGF- β receptor 1 or 2 gene in seven out of nine patients. In one family the results of DNA analysis are still pending.

Mutation analysis

DNA analysis of the *TGFBR1* and *TGFBR2* genes was performed by direct DNA sequencing of genomic

DNA, using the BIG Dye version 3 dye terminator kit (Applied Biosystems, Torrance, CA, USA). Primer sequences are available on request.

Results

Clinical and genetic evaluation

Index patient A was a 21-year-old woman (figure 1) who was referred for a Marfanoid habitus. Echocardiographic assessment revealed an aortic root aneurysm and an impaired left ventricular function with hypokinetic apical and septal regions. In addition, the pulmonary artery was dilated (figure 2). Further clinical characteristics are summarised in table 2. DNA sequencing revealed a previously described missense mutation c.1609C>T (p.Arg537Cys)⁶ in the TGF- β receptor 2 gene. It could not be found in her parents, implying a *de novo* mutation.

Index patient B was a 4-year-old boy (figure 3) who was referred for a syndromal diagnosis. At birth, a cleft palate with a bifid uvula and a windmill deformity of his left foot were diagnosed (figure 4) and, at age 4 months, an aortic root aneurysm was also found. His clinical characteristics are listed in table 2. DNA sequencing

Figure 1. Patient A: this patient did not demonstrate typical craniofacial characteristics of LDS type 1, e.g. hypertelorism, cleft palate, bifid uvula or malar hypoplasia. In the lateral view, only a slight retrognathia can be recognised. Reproduced with the patient's permission.

Figure 2. Echographic image (parasternal short-axis view) in patient A demonstrating marked dilatation of the pulmonary artery, including the root, the trunk and the branches (a. pulmonalis sinistra and dextra). Dimensions were 2.9 cm, 2.7 cm, 1.4 cm and 1.4 cm, respectively, which is too large relative to the limited body surface area.

revealed a novel c.1051G>C (p.Asp351His) mutation in the TGF- β receptor 1 gene. Genetic screening in his parents did not find the mutation, implying a *de novo* mutation.

Index patient C was a 23-year-old woman who was evaluated in our clinic in 1999 because of a family history of aortic dissection. Her mother suffered from an acute type A aortic dissection at the age of 40 years and died from a ruptured abdominal aneurysm three years later. Patient C did not meet the formal MFS (Ghent) criteria⁷ but did show an aortic root aneurysm. In addition, she had a cleft palate. Her characteristics

Figure 3. Patient B demonstrating several facial abnormalities: malar hypoplasia, long philtrum and thin upper lip (although none are specific for LDS). Reproduced with the permission of the patient's parents.

Figure 4. Left foot of patient B demonstrating a windmill deformity.

are given in table 2. Her brother (C-II) was also evaluated in our clinic at the age of 19 years. The diagnosis of aortic root aneurysm had been made in this patient and he also had a cleft palate. His clinical characteristics are listed in table 2. He underwent a Bentall procedure at the age of 22 years because of an aortic root aneurysm of 51 mm and experienced a myocardial infarction shortly after surgery due to an unknown cause. A computed tomography (CT) scan of the coronary arteries did not reveal any explanation for the myocardial infarction but did show a rapid tapering of the right coronary artery and the left anterior descending coronary artery. At the age of 24 years he died suddenly during physical activity. DNA sequencing is pending.

Index patient D was a 42-year-old man who presented along with his 6-year-old daughter and his 3-year-old son. At the age of 33 years he underwent an aortic valve replacement for severe aortic insufficiency. Two years later he had a reoperation because of an aortic root aneurysm of 52 mm. He did not fulfil the MFS (Ghent)

Table 2. Clinical characteristics of our nine patients.

Typical features	Patients										Prevalence in this study	Prevalence (%) according to Loeys et al. ⁴ LDS type 1/2
	A	B	C	C-II	D	D-II	D-III	D-IV	D-V	(n=9)	(n=40/n=12)	
Hypertelorism ^e	-	-	-	-	-	-	-	-	-	0/9	90/0	
Cleft palate	-	+	+	+	-	-	-	-	-	3/9	90/0	
Bifid or abnormal uvula	-	+	+	+	+	+	+	+	-	7/9	90/25	
Aortic root aneurysm	+	+	+	+	+	+	+	+	+	9/9	98/100	
Arterial tortuosity	-	-	ND	ND	ND	ND	ND	ND	ND	0/2	84/67	
Aneurysm of other vessels	+*	-	ND	+**	ND	ND	ND	-	-	2/5	52/73	
Craniofacial												
High arched palatum	-	-	+	+	-	-	-	-	-	2/9	Not reported	
Dental crowding	+	-	+	+	-	-	+	+	+	6/9	Not reported	
Malar hypoplasia	-	+	+/-	+	-	-	-	+	-	4/9	60/0	
Retrognathia ^g	+/-	+	-	-	-	-	-	+	+	2/9	50/0	
Craniosynostosis ^d	-	-	-	-	-	-	-	-	-	0/9	48/0	
Blue sclerae	-	+/-	-	-	-	+/-	+/-	+/-	+/-	5/9	40/0	
Ectopia lentis ^f	-	-	-	-	-	-	-	-	-	0/9	0/0	
Skeletal												
Dolichostenomelia ^b	-	-	+	-	-	-	-	+	-	2/9	18/0	
Arachnodactyly ^a	-	-	-	-	-	-	-	-	-	0/9	70/0	
Pectus deformity	+	+	+	+	+	-	-	-	-	5/9	68/0	
Scoliosis	+/-	-	-	-	-	-	-	+	+	1/9	50/0	
Joint laxity	-	+	+	-	-	+	+	-	-	4/9	68/100	
Talipes equinovares ^c	-	+	-	-	-	-	-	+	-	2/9	45/0	
Cardiac												
Mitral valve prolapse	-	-	-	-	+	-	-	-	-	1/9	Not reported	
Atrial septal defect	+	-	-	-	-	-	-	-	-	1/9	22/0	
Cutaneous												
Velvety skin	-	-	-	-	-	-	-	+	+	2/9	28/82	
Translucent skin	-	+	-	-	+	+	+	-	-	4/9	32/64	
Other												
Fulfilling Ghent criteria ⁷	-	-	-	-	-	-	-	-	-	0/9	0/0	

ND=not determined, * pulmonary artery, ** abdominal aorta, ^a long slender fingers, ^b thin body habitus and long extremities, ^c clubfeet, ^d premature closure of cranial sutures, ^e increased distance between pupils, ^f lens subluxation, ^g recessed jaw.

criteria and had a bifid uvula. His 6-year-old daughter (D-II) had a congenital joint dislocation of her right hip. In addition, she had an aortic root aneurysm and a bifid uvula (figure 5). His 3-year-old son (D-III) also had a bifid uvula. Further characteristics of these subjects are given in table 2. The brother (D-IV) of the index patient (D) had undergone a Bentall procedure and a partial aortic arch replacement because of aneurysms of these parts of the aorta. He was born with pes equinovares (clubfeet) and underwent surgery for bilateral inguinal hernia. His daughter (D-V) also has an inguinal hernia and mild scoliosis. The mother of D and D-IV died of the consequences of a ruptured type B aortic dissection when she was 56 years of age.

In all the patients from family D we identified a c.1609C>T (p.Arg537Cys) mutation in the TGF- β receptor 2 gene, conforming a diagnosis of LDS.

Discussion

In 2005 Loeys and Dietz described a new autosomal dominantly inherited disorder of connective tissue which shares many similarities with MFS and the vascular type of EDS (table 1).^{3,4} However, there are apparent phenotypic differences which are important for both the recognition and treatment of the syndromes. Typical and easily recognisable characteristics that distinguish LDS type 1 from MFS are hypertelorism (increased distance between the pupils), cleft

Figure 5. Patient D-II demonstrating a bifid uvula, one of the typical characteristics of LDS. This characteristic was also seen in patients B, C, C-II, D and D-III.

palate or bifid uvula, generalised arterial tortuosity, craniosynostosis (premature closure of cranial sutures), patent ductus arteriosus and atrial septal defect, whereas LDS type 2 patients demonstrate skin abnormalities (easy bruising, translucent velvety skin), joint laxity and rupture of visceral organs (see also tables 1 and 2).^{3,4} Ectopia lentis (lens subluxation), which can be found in 40 to 56% of patients with MFS, as well as other ocular manifestations are absent in LDS.^{3,4,8} However, LDS is clinically highly variable, as demonstrated by our nine patients with LDS.⁹ This variability may hamper proper classification in the two subtypes of the syndrome. Note, for example, the differences between patients A and B (table 2, figures 1, 2 and 3). Remarkably, none of our patients demonstrated hypertelorism (increased distance between pupils) or craniosynostosis (premature closure of cranial sutures), which are allegedly encountered in 90 and 50% of LDS type 1 patients, respectively.⁴ In addition, although it has not yet been systematically evaluated in all our patients, arterial tortuosity was not found in our group. These examples underscore the wide clinical variability and the need for a critical evaluation of all patients presenting with one of the symptoms of the syndrome.

Patients with LDS type 1 tend to require earlier cardiovascular surgery and have a shorter life expectancy than those with LDS type II.⁴ However, it should be kept in mind that all LDS patients show aggressive vascular disease and thus all require careful follow-up and management; we will discuss this later. Patients suspected of having LDS should undergo a physical examination, paying special attention to the typical characteristics of LDS, echocardiographic assessment and genetic testing for TGF- β receptor 1 and 2 gene mutations.

An altered signalling of the TGF- β cytokine family, which plays an important role in cell proliferation and

differentiation, apoptosis and extracellular matrix formation, underlies both LDS and MFS.^{10,11} The altered TGF- β signalling causes disarrayed elastic fibres and loss of elastin content in the aortic media, predisposing to dilatation and dissection of the aortic wall.³ In MFS an abnormal fibrillin protein causes an increased activity of TGF- β and this leads to the typical phenotypic characteristics of the disease.¹¹ However, in LDS, disruption of the normal TGF- β signalling takes place at the level of the TGF- β receptors.³ Mutations in either the TGF- β receptor 1 or 2 genes have been identified in one-third and two-thirds of LDS patients, respectively.^{3,4}

As TGF- β molecules also play an important role in cardiovascular embryogenesis, including guidance of the formation of the ventricular myocardium, mutations in the TGF- β receptors could well have an effect on ventricular function and might underlie the impaired left ventricular function with hypokinetic apical and septal regions in patient A, a feature which has not been described in patients with LDS.¹²

The recognition of LDS is especially important from a management point of view. Cardiovascular disease seems to be more aggressive and widespread in LDS than in MFS. Recently, Williams et al.⁵ reported aortic rupture and dissection in young patients and in patients with aortic root diameters not considered at risk in MFS (<4.5 cm); in addition they reported high rates of repeat surgical interventions. Furthermore, aneurysms were not confined to the aortic root but occurred throughout the entire arterial tree.^{5,13}

The above observations have important clinical consequences for patients with LDS. Firstly, after establishing the diagnosis, regular repeated echocardiographic assessment should be performed, paying particular attention to the aortic root diameter and the growth of this diameter. In addition, patients should undergo MR angiography from head to pelvis to discover other possible aneurysms.⁵ Secondly, when an aortic root aneurysm is found, β -blockade therapy should be initiated to reduce further dilatation. Alternatively, LDS patients might benefit more from losartan, an angiotensin II receptor antagonist, as this drug antagonises TGF- β and has proven to be effective in mouse models of MFS.¹⁴ Thirdly, surgical intervention should probably be considered earlier than in MFS. Current recommendations for adult and paediatric patients, as proposed by Williams et al., are summarised in table 3.⁵ However, it should be noted that these recommendations were not empirically established. Since little is known about the natural history of the syndrome, these are the only recommendations currently available. Earlier intervention should be considered based upon the family history or an assessment of risk versus benefit for an individual patient.

Although vascular disease is aggressive in LDS, patients do not have friable vascular tissue, unlike the vascular type of EDS, and they appear to tolerate

Table 3. Indications for surgical intervention in Loeys-Dietz syndrome.***Adults**

- a. Aortic root >4.0 cm or expanding rapidly (>0.5 cm/year)
- b. Descending thoracic aorta >5.0 cm or expanding rapidly (>0.5 cm/year)
- c. Abdominal aorta >4.0 cm or expanding rapidly (>0.5 cm/year)
- d. Rapid expansion of peripheral aneurysms

Children

- a. 1. Severe craniofacial features: aortic root z-score >3.0 or expanding rapidly (>0.5 cm/year)
2. Mild craniofacial features: aortic root z-score >4.0 or expanding rapidly (>0.5 cm/year)
- b. Effort should be made to delay surgery until the annulus reaches 1.8 cm, allowing placement of a valve-sparing graft of sufficient size to accommodate growth
- c. Large size or rapid expansion of the descending aorta or other vessels

*Derived from Williams et al.⁵

surgery well in an elective setting.^{5,15} After surgical intervention, follow-up should be continued and regular imaging of the entire arterial tree should be performed so that new arterial pathology can be recognised and treated in good time.

Conclusion

We have described nine LDS patients and discussed important aspects concerning the diagnosis and management of the disease. Every cardiologist and cardiothoracic surgeon, particularly those specialising in aortic pathology, should be aware of this newly recognised syndrome. Young patients presenting with aortic dissection, aortic root aneurysm, or aneurysms elsewhere should be evaluated for LDS. A simple physical examination – checking for hypertelorism, cleft palate or bifid uvula and skin abnormalities – can provide important clues to the presence of the syndrome. Given the potentially aggressive nature of LDS, careful follow-up and early surgical intervention are mandatory.

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