Cardiovascular involvement and prognosis in Loeys-Dietz syndrome

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ABSTRACT

Background: Loeys-Dietz syndrome (LDS) is an inherited connective tissue disorder associated with aortic root enlargement and risk of thoracic aortic dissection (AD). Genetic examination is essential for diagnosis.

Aims: The study aimed at analysis of clinical data on cardiovascular involvement and management of LDS patients.

Methods: The study included carriers of LDS-associated genetic variants, identified between 2012 and 2022. Assessment of cardiovascular involvement was based on echocardiography and computed tomography angiography with quantitative assessment of arterial tortuosity. Involvement of other systems was also evaluated. We noted major cardiovascular events, including aortic events, defined as AD, elective aortic surgery, or otherwise unexplained sudden death.

Results: Thirty-four patients from 15 families were included, and five identified variants were novel. Probands' mean age was 41 years. Cardiovascular abnormalities, aortic involvement, aortic tortuosity, and tortuosity of cervical arteries were present in 79%, 71%, 68%, and 100% of carriers, respectively. First aortic events (9 A-type AD, 6 elective thoracic aortic surgeries, and one sudden death) occurred in 16 (47%) patients at a median age of 35 years. The youngest age at AD was 16 years, and 7 years for elective aneurysm repair. Second and third aortic events occurred in 9 and 4 patients, respectively. Eight patients (24%) experienced other major cardiovascular events. Aortic event-free survival was shorter in the presence of skin striae ($P = 0.03$), tended to be shorter in the presence of Marfanoid features ($P = 0.06$), and longer with *TGFB2* variants ($P = 0.06$).

Conclusions: LDS is associated with high burden of cardiovascular complications at a young age.

Key words: Loeys-Dietz syndrome, next-generation sequencing, thoracic aortic aneurysms and dissections

INTRODUCTION

Heritable thoracic aortic aneurysms and dissections (TAAD) comprise transforming growth factor β (TGFβ) pathway-related syndromes. The most common of these is Marfan syndrome (MFS), others include Loeys-Dietz syndrome (LDS), Shprintzen-Goldberg syndrome, and the recently recognized Meester-Loeys syndrome [1]. Other rare syndromic forms of heritable TAAD involve *COL3A1*-related vascular Ehlers-Danlos syndrome, *LOX*-related TAAD, and smooth muscle dysfunction syndrome related to *ACTA2* variants [1].

LDS is a connective tissue disorder associated with increased risk of thoracic aortic

WHAT'S NEW?

This study broadens knowledge about the genetic background of Loeys-Dietz syndrome (LDS) with identification of novel pathogenic variants in LDS-associated genes. It is the first study assessing quantitatively arterial tortuosity of both cervical arteries and the aorta in LDS. We show significant morbidity and mortality in LDS patients. Attempts to identify adverse prognostic factors showed that patients with Marfanoid habitus had a trend towards shorter aortic event-free survival and, in particular, LDS variant carriers with skin striae had worse aortic event-free survival.

dissection (AD) and aneurysm rupture at an early age, often at smaller aortic diameters [2]. The cardinal cardiovascular abnormality in LDS is an aneurysm of the aortic root, which often extends into the proximal tubular aorta creating a pear-shaped aortic dilatation [3]. LDS was first described in 2005 and initially associated with *TGFBR1* and *TGFBR2* genes [2], referred to as LDS type 1 and type 2, respectively. The spectrum of LDS was gradually expanded to include cases related to variants in *SMAD3*, *TGFB2* [4–6], and recently *TGFB3* [7], described as LDS types 3–5, respectively. In this study, we aimed to assess genetic and clinical characteristics, survival, and potential risk factors in LDS patients, diagnosed genetically in our Unit, and treated in our Institute and other cardiovascular centers.

METHODS

Genetic evaluation

The study cohort consisted of carriers of LDS-associated genetic variants, which were identified in the National Institute of Cardiology, Warsaw. Genetic testing was offered to index patients referred to our Institute from 2012 to 2022 with the diagnosis of TAAD, primarily with early-onset aortic disease, suspected connective tissue disorders, family history of TAAD, and/or after thoracic aortic dissection. Whole exome sequencing was performed in 6 LDS probands [8], a custom-designed panel (SeqCap, Roche, Indianapolis, IN, US) consisting of 31 genes related to aortopathies and connective tissue disorders was used in 7 probands [9], and a commercial panel (TruSight Cardio, Illumina, San Diego, CA, US), consisting of 174 genes, including 18 TAAD-related genes, was used in the remaining 4 probands. Sequencing was performed on MiSeq Dx (Illumina). Identified variants were evaluated according to the American College of Medical Genetics and Genomics criteria [10].

In all probands a three-to-four-generation pedigree was drawn, and the family history of TAAD and other diseases was taken. Subsequent cascade screening was offered to all probands' relatives, and identified variants were followed up in relatives with Sanger sequencing.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Bioethics Committee of the National Institute of Cardiology, Warsaw, Poland. All participants gave written informed consent.

Clinical assessment

Assessment of aortic root and ascending aorta dimensions was based on echocardiography, using leading-edge-to-leading-edge convention at end diastole [11]. We used the web calculator (https://marfan.org/dx/z-score-adults/) and assumed that the aortic root was dilated with a Z-score >2.0 [12]; the remaining sections of the aorta were assessed according to the European Society of Cardiology guidelines [11]. Whenever possible, patients were referred for computed tomography angiography (CTA) of the aorta and, after LDS diagnosis, of cervical and cerebral arteries (however, some patients were treated in other cardiology centers, and were referred to our Institute for genetic assessment only). CTA examinations were performed using a 384-slice dual-source scanner (Somatom Force, Siemens, Erlangen, Germany). Both imaging modalities (echocardiography and CTA) were used to assess the presence of congenital heart defects and vascular abnormalities (dissections, aortic dilatation, and peripheral arterial aneurysms, defined as a dilatation of >50% of the diameter of the native vessel). Cardiovascular involvement was ascertained when any of the listed above abnormalities were present.

CTA was also assessed for arterial tortuosity, which was evaluated using the tortuosity index (TI), defined as the ratio of the vessel centerline length divided by the straight length, measured for the aorta, extracranial segments of internal carotid arteries, and vertebral arteries. Aortic tortuosity was ascertained when the TI exceeded 1.95 [13], and cervical arterial tortuosity was ascertained when the TI exceeded 1.1 for any vertebral and/or carotid artery [14].

Assessment of other systems was based on physical examination, imaging tests, and medical records. Revised Ghent criteria were used to assess systemic features of MFS (*inter alia,* pectus deformities, arachnodactyly, skin striae) and to calculate the Marfan systemic score [15]. We also looked for other craniofacial abnormalities (e.g., hypertelorism, cleft palate, bifid uvula, blue sclerae), skeletal findings (joint laxity, clubfoot), and cutaneous findings (easy bruising, atrophic scars, translucent, or velvety skin). Hypertension was defined as repeated blood pressure measurements ≥140/90 mm Hg or antihypertensive therapy, and smoking as any cigarettes smoked during 6 months before the initial visit.

Aortic events were defined as AD, elective thoracic aortic surgery, or unexplained sudden death, probably a result

of acute aortic syndrome in the investigator's assessment. We also recorded other major cardiovascular events not explained by comorbidities, such as peripheral artery dissection, subarachnoid bleeding, cryptogenic stroke, other acute ischemic events, or surgery due to peripheral artery aneurysm, abdominal aortic aneurysm, or congenital heart defect. Follow-up information was collected primarily during consecutive visits to the Institute. In few cases of a prolonged break in follow-up visits, information was obtained over the phone or from patients under the care of the Institute or their relatives. The follow-up period extended to the most recent evaluation before October 31, 2022.

Statistical analysis

All results for categorical variables were presented as counts and percentages and for numerical variables as means and standard deviations (SD) or medians (interquartile ranges [IQR]). The chi-square independence or Fisher's exact test were used for comparison of binary variables, and Cochran-Mantel-Haenszel general association statistics for nominal data above two categories. The differences between numerical variables were tested by Student's t-test or one-way ANOVA (for two independent samples or four groups, normally distributed data) and, in the case of skewed distribution, by non-parametric Mann–Whitney or Kruskall-Wallis tests, as appropriate. Survival curves were constructed by the Kaplan–Meier method and compared by the log-rank test. In subjects without an event, the follow-up period extended to the most recent evaluation before October 31, 2022. All hypotheses were two-tailed with 0.05 type I error. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC, US).

RESULTS

Genetics

We identified 17 rare variants in LDS-related genes in 17 unrelated probands (Supplementary material, *Table S1*). Probands with pathogenic and likely pathogenic variants and their relatives with variant carrier status were included in the study. Two probands with variants of unknown significance were excluded due to the lack of convincing evidence of their etiological significance (no systemic features, no co-segregation in the family). Five pathogenic or likely pathogenic variants were novel: a missense variant in *TGFBR1* and in *TGFBR2*, two truncating variants, and a large deletion in *SMAD3*.

Study cohort characteristics

In all, 34 patients from 15 families were included in the study. General characteristics are shown in Table 1 and Supplementary material, *Table S2,* with a comparison between probands and non-probands and among LDS types. Probands constituted 44% of the study group, their median age was 41 years, and 60% of them were male. At the time of the genetic inquest, cardiovascular abnormalities and aortic involvement were present in the vast majority of subjects (79 and 71%, respectively). Congenital heart defects included bicuspid aortic valve and patent ductus arteriosus (PDA) in a p.Thr530Ile *TGFBR2* variant carrier, PDA in a p.Pro351Leu *TGFB2* variant carrier, as well as atrial septal defect in 4 patients, bicuspid aortic valve (1 patient), and partial anomalous pulmonary venous return (1 patient), all found in a previously described p.Arg460His *TGFBR2* family [16]. Peripheral artery aneurysms were present in nearly

Table 1. Phenotypic characteristics at the time of genetic inquest

	All (n = 34)	Probands (n = 15)	Relatives (n = 19)	*P*-value
Age, years, median (IQR)	32 (23–43)	41 (27–50)	26 (15–42)	0.08
Male sex, n (%)	19 (56)	9 (60)	10 (53)	0.67
Cardiovascular involvement, n (%)	27 (79)	15 (100)	12 (63)	0.01
Thoracic aortic dilatation, n (%)	24 (71)	15 (100)	9 (47)	<0.001
Aortic root, mm, median (IQR)	40 (36–47)	44 (42–48)	36 (33–40)	<0.001
Ascending aorta, mm, median (IQR)	32 (27–42)	42 (33–49)	28 (25–32)	0.001
Peripheral artery aneurysm (n = 31) , n (%)	7 (23)	4 (27)	3 (19)	0.69
Aortic TI (n = 25), mean (SD)	2.07 (0.26)	2.10 (0.22)	2.05 (0.29)	0.62
Aortic TI >1.95, n (%)	17 (68)	8 (73)	9 (64)	1.00
Vertebral TI (n = 14), mean (SD)	1.46 (0.20)	1.40 (0.17)	1.48 (0.22)	0.58
Internal carotid TI (n = 14), mean (SD)	1.28 (0.16)	1.20 (0.13)	1.30 (0.16)	0.33
Marfan systemic score, points, median (IQR)	3 (1–6)	3 (1–7)	3 (1–5)	0.40
Marfan systemic score ≥7 points, n (%)	6 (18)	4 (27)	2 (11)	0.37
Craniofacial anomalies, n (%)	16 (47)	7 (47)	9 (47)	0.97
Skeletal findings, n (%)	26 (77)	11 (73)	15 (79)	1.00
Thorax deformities, n (%)	20 (59)	10 (67)	10 (53)	0.41
Cutaneous manifestation, n (%)	20 (59)	10 (67)	10 (53)	0.41
Skin striae, n (%)	10 (29)	7 (47)	3 (16)	0.07
Hypertension, n (%)	13 (38)	8 (53)	5 (26)	0.11
Smoking, n (%)	7 (21)	3 (20)	4 (21)	1.00

Abbreviations: IQR, interquartile range; SD, standard deviation; TI, tortuosity index

Table 2. Cardiovascular outcome at the time of last follow-up

	All (n = 34)	Probands (n = 15)	Relatives (n = 19)	*P*-value	*TGFBR1* (n = 7)	*TGFBR2* (n = 15)	*SMAD3* (n = 7)	*TGFB2* (n = 5)	*P*-value
Age, years, median (IQR)	36 (27–51)	43 (31–54)	32 (23–49)	0.12	38 (32–62)	32 (25–51)	43 (27–51)	39 (32–41)	0.62
Patients with aortic events, n (%)	16 (47)	12 (80)	4 (21)	<0.001	4 (57)	8 (53)	4 (57)	0	0.17
Age at first aortic event, years, median (IQR)	35 (27–44)	35 (23–44)	34 (30–48)	0.76	40 (26–46)	30 (22–38)	39 (32–50)	–	0.50
Number of aortic events per patient, mean (SD)	0.8 (0.2)	1.1 (0.3)	0.3 (0.1)	<0.001	1.3 (0.5)	0.9 (0.3)	1.0 (0.4)	0	0.18
Patients with thoracic aortic dissection, n (%)	10 (29)	9 (60)	1 (5)	0.002	3 (43)	4 (27)	3 (43)	0	0.36
Age at aortic dissection, median (IQR)	42 (36–46)	40 (36–46)	59 (59–59)	0.16	46 (37–46)	34 (22–50)	43 (36–58)	–	0.69
Patients with major CV events, n (%)	19 (56)	12 (80)	7 (37)	0.01	4 (57)	10 (67)	4 (57)	1 (20)	0.36
Number of major CV events per patient, mean (SD)	1.2 (0.2)	1.9 (0.3)	0.5 (0.2)	<0.001	1.3 (0.5)	1.3 (0.4)	1.3 (0.5)	0.2 (0.2)	0.31
CV or unexplained death, n (%)	6 (18)	3 (20)	3 (16)	1.00	1 (14)	3 (20)	2 (29)	0	0.64

Abbreviations: CV, cardiovascular; other — see Table 1

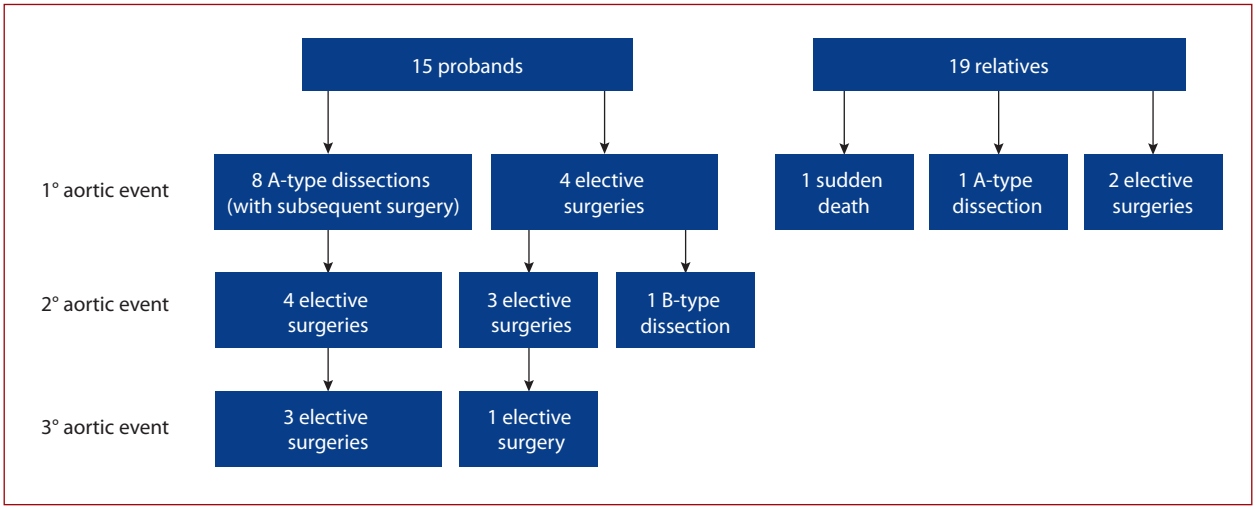

Figure 1. Aortic events in the study cohort of patients with Loeys-Dietz syndrome

one-fourth of carriers in various locations (basilar, carotid, vertebral, subclavian, hepatic, and iliac arteries).

Increased arterial tortuosity measured by the TI was found in all examined patients in the cervical arteries with a cut-off value of 1.1 and in 68% of patients in the aorta with a cut-off value of 1.95.

Involvement of other systems was common: skeletal findings were present in 77% of patients, craniofacial in 47% (including cleft palates in two cases), and cutaneous in 67%. Systemic features attributed to MFS were found commonly (with a median systemic score of 3). Notably, 6 (18%) carriers fulfilled the criteria for the diagnosis of MFS with a systemic score ≥7 points (and in fact, several had the diagnosis of MFS made). No patients had osteoarthritis.

Outcome and prognostic factors

Major cardiovascular events in the study cohort of LDS patients are summarized in Table 2. The most common adverse events were associated with aortic pathology. They occurred in 16/34 (47%) cases at the median age of 35 years, and half of them were recurrent (Figure 1).

Among first aortic events, there were 9 cases of A-type AD (all before LDS diagnosis) and 6 elective surgeries due to ascending aortic aneurysm; we also included a sudden death of a 36-year-old patient awaiting surgery for a thoracic aortic aneurysm. Aortic root measurements preceding dissection were available in 7 subjects and ranged from 40 to 51 mm, the median diameter was 47 (42–50) mm. A detailed description of the events is included in the Supplementary material, *Table S3*.

The median cumulative risk (50%) of an aortic event in all LDS variant carriers was at the age of 46 years. At the age of 59 years, cumulative risk reached the rate of 80%.

TGFB2 variant carriers tended to have longer aortic event-free survival than *TGFBR1/2* or *SMAD3* variant carriers ($P = 0.06$; Figure 2). We found a trend towards shorter event-free survival in LDS variant carriers who had Marfan systemic score ≥7 ($P = 0.06$). Interestingly, the presence of easily identified skin striae was a significant predictor

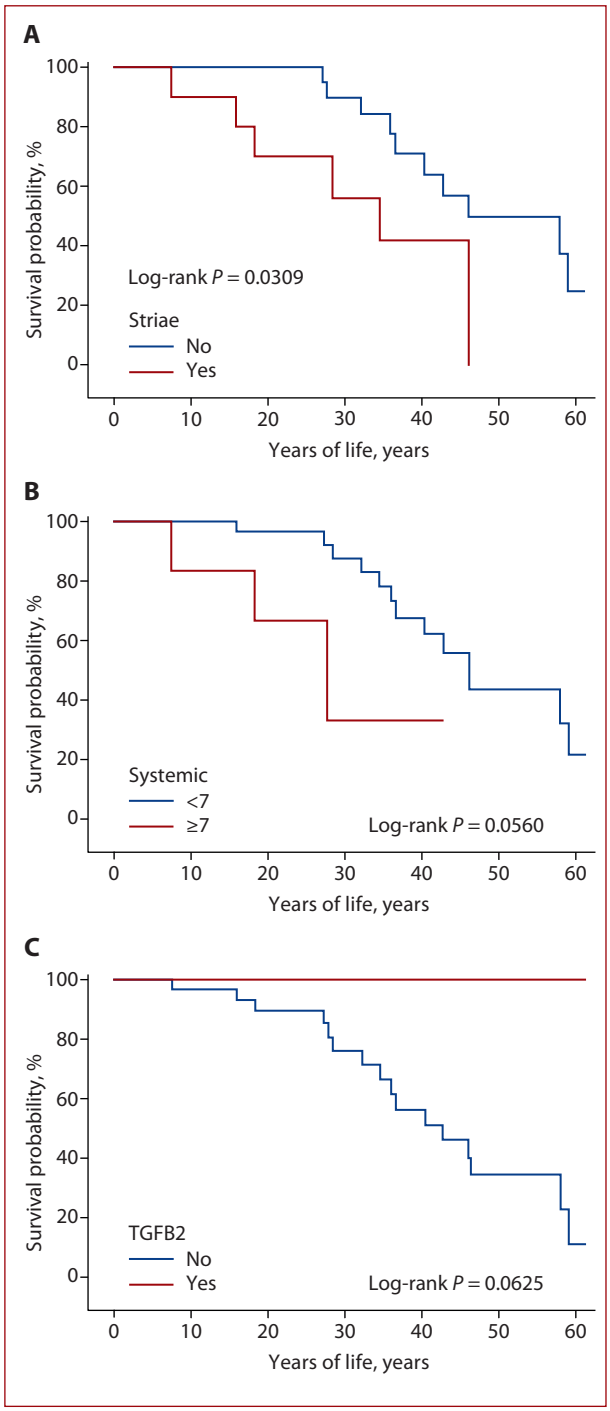

Figure 2. Kaplan–Meier aortic event-free survival curves during lifespan in patients with Loeys-Dietz syndrome-associated variants according to **A.** presence of skin striae; **B.** Marfan systemic score; **C.** Presence of variants in *TGFB2* vs. other genes

of worse aortic event-free survival ($P = 0.03$) in the study cohort (Figure 2).

Eight patients experienced other major cardiovascular events, including atrial septal defect closure surgery, PDA occlusion, peripheral aneurysm stent-graft implantation, elective abdominal aortic repair (in a 46-year-old woman), dissection of both coronary arteries, subarachnoid bleeding, and cryptogenic stroke.

During the median follow-up time of 5.6 (2.8–8.6) years, 6 patients (18%) died at a median age of 51 (37–60) years: one death was sudden, one from remote ischemic complications of dissected abdominal aorta, one due to end-stage heart failure, and as many as three cases due to complications in the perioperative period.

DISCUSSION

This study provides new clinical information on LDS patients including quantitative assessment of cervical arteries and aortic tortuosity. We also show high morbidity and mortality in that setting and indicate new potential risk factors for aortic events.

A prominent phenotypic feature of LDS is arterial tortuosity, assessed, in particular, within the head and neck, and also in relation to the aorta. In our study group, all patients assessed with CTA had vertebral and/or carotid artery tortuosity. Using a similar methodology, Morris et al. [14] assessed vertebral arteries by magnetic resonance angiography in 90 patients with connective tissue disorders. The vertebral TI was significantly higher in patients with MFS (n = 57) and LDS (n = 13) in comparison to controls (median values of 1.26, 1.58, and 1.05, respectively; values adjusted according to the formula used in our study). Increased vertebral TI values of 1.11–1.49 and ≥1.5 were associated with shorter surgery-free survival (adjusted hazard ratio, 10.6 and 29.6, respectively). In turn, Welby et al. evaluated carotid artery tortuosity by the presence of loops, kinks, or coils in 143 patients with connective tissue disease and 143 controls [17]. Carotid artery tortuosity rates were 88% for MFS (n = 33) and 63% for LDS (n = 16). The combination of aortic aneurysm and carotid artery tortuosity strongly indicated connective tissue disease with a positive predictive value of 95% and specificity of 99%.

We used analogous quantitative methodology to assess the tortuosity of the aorta. Increased aortic tortuosity with the TI >1.95 was present in 68% of our patients. The cut-off value of 1.95 was an indicator of worse prognosis in MFS in a study by Franken et al. [13]. Moreover, aortic tortuosity, along with hypertelorism and wide scars, was associated with higher risk of AD, when assessed in the cohort of 214 *TGFBR1/2* patients; however, the definition of aortic tortuosity was not presented [18].

Overall, almost half (47%) of our patients had aortic events, the majority of them recurrent. In LDS patients, prophylactic aortic root replacement prevents A-type AD and improves outcomes [1, 18]. Importantly, AD may occur at smaller aortic dimensions [1, 18, 19]. In our study, the median aortic root dimension preceding dissection was only 47 mm. It demonstrates the significance of the latest American and European guidelines, advising prophylactic aortic surgery at aortic root diameter ≥4.5 cm, or even earlier in the presence of high-risk features [1, 20].

The median age at the time of AD was 42 years. Notably, in the first study on *TGFBR1/2*-related aneurysmal disease,

the mean age at first vascular dissection was only 27 years, with the majority of events affecting the proximal aorta [6]. In the more recently published GenTAC registry, the median age at AD was 38.5 years in LDS type 1 and 35.5 years in LDS type 2 [21].

Similar to our study, LDS has been associated with the rapid progression of aortic aneurysmal disease, also after AD [22–25]. Multiple aortic interventions in LDS patients have been reported in surgical series [23, 26] and in a recently published study on patients with heritable TAAD [25]. To address a more aggressive course of aortic disease in LDS patients, Maleszewski et al. examined histopathologically aortic samples and found significantly more diffuse and less "cystic-type" degeneration of the aortic media, compared to MFS [27].

Singh et al. re-examined MFS patients with screening for *TGFBR1* or *TGFBR2* variants and revealed an extensive clinical overlap between patients with MFS and LDS [28]. In our study, 6 (18%) carriers had features of MFS with systemic score ≥7, which was associated with a trend towards worse prognosis. Furthermore, the presence of skin striae was associated with significantly shorter aortic event-free survival ($P = 0.03$). Interestingly, there was a report of simultaneous surgical treatment of a chest deformity and aortic dilatation in a patient with LDS [29].

Another interesting issue in LDS is marked intrafamilial variability, which concerns not only aortic disease but also a variety of vasculopathies and congenital heart defects. Tran-Fadulu et al. found that in families with *TGFBR1* variants, men presented with TAAD and women often with dissections and aneurysms of arteries other than the ascending thoracic aorta [30]. Similarly, in our recently reported family with the p.Arg460His *TGFBR2* variant, we found a huge variability in cardiovascular phenotype [16].

In conclusion, our study underlines significant morbidity and mortality in LDS patients. We present novel pathogenic variants in LDS genes and show the utility of quantitative assessment of arterial tortuosity, common in LDS. Awareness of the syndrome and early diagnosis are crucial to provide optimal medical and surgical care for the patients. As long as causative treatment is unavailable, lifestyle modification and correction of modifiable cardiovascular risk factors, in particular, hypertension treatment and smoking cessation, are of paramount importance. All patients should have a rigorous imaging follow-up of the arterial tree, especially of the aorta.

Article information

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