Loeys-Dietz syndrome: Intermediate-term outcomes of medically and surgically managed patients

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ABSTRACT

Objectives: Loeys-Dietz syndrome (LDS) is an aggressive connective tissue disorder associated with increased risk of aortic dissection and aneurysm rupture at an early age and smaller aortic diameters. We report our experience with LDS to better understand its natural history and treatment outcomes and help establish treatment guidelines.

Methods: We retrospectively reviewed all patients with LDS who underwent medical or surgical treatment at Cleveland Clinic before April 27, 2017. Primary endpoints were postoperative in-hospital morbidity and mortality. Secondary endpoints were aorta-related reoperations and short- and long-term mortality.

Results: We identified 53 patients with LDS. Of these, 33 (62%) underwent aortic surgery. Mean age was 39 ± 14 years, and mean maximum aortic diameter was 4.3 cm. There were 2 (6%) deaths after urgent or emergency surgery. Twenty-two patients (67%) required no aortic reoperation; 20 of these had prophylactic surgery. Multiple aortic operations were performed on 11 (33%) patients, 9 of whom experienced aortic dissections. Six patients (18%) required total aortic replacement. Among 19 patients with modified root reimplantation, no aorta- or valve-related complications occurred. Overall, 33 patients underwent 58 aortic and 81 cardiovascular operations, with 1 late death. Kaplan-Meier survival of the aortic-surgery cohort was 89% at 10 years (median follow-up 5.2 years). There were no late deaths in the non-aortic surgery group (20/53; 38%).

Conclusions: Prophylactic aortic surgical outcomes in LDS are excellent. Surgical reintervention remains high, particularly after aortic dissections. Close surveillance of medically managed and postoperative patients and early prophylactic surgery are crucial to avoid aortic catastrophe and achieve a good long-term prognosis. (*J Thorac Cardiovasc Surg* 2019;157:439-50)

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Central Message

Loeys-Dietz syndrome carries a malignant prognosis, with early presentation of aortic dissection and rapid progression of aneurysmal dilatation if not treated before dissection occurs.

Perspective

Intermediate-term outcomes of prophylactic aortic surgery for Loeys-Dietz syndrome (LDS) are excellent. Surgical reintervention remains common, particularly after aortic dissections. Early prophylactic surgery and close surveillance of the distal aorta in LDS patients, both with and without dissection, are necessary to achieve a good long-term prognosis.

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Connective tissue disorders are increasingly being recognized and studied for their cardiovascular consequences.¹ It is incumbent on cardiologists and surgeons to better understand and manage patients with connective tissue disorders,

particularly the more recently defined ones, such as Loeys-Dietz syndrome (LDS). LDS was identified in 2005 as an autosomal-dominant connective tissue disorder caused by mutation in transforming growth factor β receptor-1

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Abbreviations and Acronyms

CTA	= computed tomographic angiogram
LDS	= Loeys-Dietz syndrome
MRI/MRA	= magnetic resonance imaging/ angiography
TAAA	= thoracoabdominal aortic aneurysm
TEVAR	= thoracic endovascular aortic repair
TGFB2	= transforming growth factor β 2 ligand gene
TGFB1	= transforming growth factor β receptor- 1
TGFB2	= transforming growth factor β receptor- 2

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(*TGFB1*) and transforming growth factor β receptor-2 (*TGFB2*) genes. Phenotypically, LDS is characterized by aortic aneurysms with generalized arterial tortuosity, cardiomyopathy, skin laxity and translucency, hypermobility, hyperlordism, pectus, craniosynostosis, and bifid or broad uvula or cleft palate.¹⁻³ After the initial description of LDS, gene mutations in *SMAD3*, transforming growth factor β 2 ligand 2 and 3 (*TGFB2* and *TGFB3*) were also noted to present with phenotypical features of LDS, particularly a very aggressive vascular disease.⁴⁻¹⁰ There is a wide spectrum of clinical variability and heterogeneity of aortic involvement among individuals with these gene defects. Extensive basic and clinical research on LDS has resulted in a better understanding of its genetic basis, clinical manifestations, classification, and treatment recommendations.¹

There is a paucity of data regarding the surgical outcomes of patients with LDS. We report our experience with LDS to clarify its natural history and outcomes of surgical intervention, and to help establish treatment guidelines for patients with LDS.

PATIENTS AND METHODS

During the past decade, we developed a registry of patients with LDS at the Aorta Center in the Heart and Vascular Institute at Cleveland Clinic. We performed a retrospective review of all patients entered in this registry before April 24, 2017 (Figure 1). Entry into the study was based on genetically confirmed diagnosis of LDS and the patient establishing care at our institution for either medical management or surgical treatment. Some of these patients were evaluated and treated before the confirmed diagnosis of LDS. Later genetic testing and confirmation of phenotypic

features established their diagnosis. Some patients had previous surgical interventions at other institutions.

For this report, the first surgical procedure performed at our institution was considered the index operation. Conduct of this study was approved by the Cleveland Clinic Institutional Review Board, with patient consent waived.

Patients are classified into 2 groups based on their treatment history. The aortic surgery group consists of those who underwent aortic surgery either at our or an outside institution. The non-aortic surgery group includes patients who did not undergo any aortic surgical procedure in their lifetime and were treated medically with ongoing clinical and radiologic surveillance. Two patients in this group had nonaortic cardiac operations performed at another institution, including an atrial septal defect repair in 1 patient and ligation of patent ductus arteriosus in another. The mainstay of medical treatment consists of aggressive blood pressure control using angiotensin receptor blockers or angiotensin-converting enzyme inhibitors and β -blockers to minimize the aortic wall stress affected by the velocity of ventricular contraction (dP/dT). Clinical and radiologic surveillance includes yearly computed tomographic angiography (CTA) combined with echocardiography or magnetic resonance imaging/angiography (MRI/MRA) to assess valvular function and the entire arterial tree from the neck through the pelvis. Additional imaging was performed as needed in patients requiring surgery. The threshold of aortic size greater than 4.2 cm or rate of growth greater than 0.5 cm/year was used as an indication for surgical intervention, per the guidelines for managing patients with LDS.¹¹

Endpoints

Primary endpoints were postoperative in-hospital morbidity and mortality. Secondary endpoints were aorta-related reoperations and long-term mortality.

Data Collection, Patient Variables, and Statistics

Clinical information was extracted from hospital medical records, operative reports, discharge summaries, and outpatient clinic records. Data included patient demographics, gene mutation, medical and surgical history, family history of aortic disease, preoperative cardiovascular imaging, including echocardiogram, computed tomography, MRI/MRA, LDS phenotypic abnormalities, surgical indications and operative details, major postoperative complications, need for reoperation, acute dissection, and death.

Categorical variables are summarized as *n* (%), and continuous variables are summarized as median with first (Q1) and third (Q3) quartiles or mean $\pm$ standard deviation. Survival and freedom from intervention were determined using the Kaplan-Meier method. The Wilcoxon chi-squared statistic was computed to test differences between groups, and *P* < .05 was considered statistically significant. Statistical analysis was performed using JMP Pro 13.0 (SAS Institute, Inc., Cary, NC).

Follow-up Data

Follow-up data were obtained from clinic visits, review of medical records, and imaging. Follow-up was 100% complete, with data being collected through the latest follow-up visit.

Operative Technique

Our operative technique for aortic root replacement, including an L.G.S.-modified valve-sparing root reimplantation using pledgets, sizing according to body surface area, and Hegar dilators, has been described previously.¹² For the composite valve-graft root replacement, we used a standard technique of root replacement with coronary button implantation. In some reoperations, an 8-mm graft to the left main coronary artery was used. Circulatory arrest was used for aortic arch replacement, and separate bypasses were created for the individual arch branch vessels to minimize late risk of patch aneurysms. Our technique for total arch replacement with elephant trunk, brain protection, and second-stage elephant trunk completion has been described previously.^{13,14} In addition, our technique for descending thoracic aortic and thoracoabdominal aortic replacement has been published previously.¹⁵ A commercially available, 4-branched graft was used for

FIGURE 1. Study cohort selection. This flow diagram summarizes the medical and surgical treatment of 53 patients with Loeys-Dietz syndrome. *The first surgical procedure performed at our institution was considered the index operation. ¶One patient who was initially medically managed underwent an elective root reimplantation during follow-up. *LDS*, Loeys-Dietz syndrome.

thoracoabdominal aortic aneurysm (TAAA) repair, and individual bypasses were created to all visceral vessels, avoiding the risk of late patch aneurysm.

RESULTS

We identified 53 patients with LDS. Of these, 33 patients (62%) constituted the aortic surgery group. The index aortic operation was performed on 31 patients at Cleveland Clinic between September 1998 and April 2017. Some earlier patients in the series did not have the LDS diagnosis before surgery. Later, the diagnosis was confirmed with phenotype and genetic testing. Mean ages at the index operation and first aortic intervention were 39 ± 15 and 37 ± 14 years, respectively. Four patients were age 18 years or younger at the first aortic surgery.

Eleven patients (33%) in the aortic surgery group developed aortic dissection. Three patients experienced new recurrent aortic dissection, all involving the descending thoracic and thoracoabdominal aorta. One patient had a previous type II dissection repair with aortic root and total arch replacement with elephant trunk procedure. The remaining 2 patients initially experienced a DeBakey type IIIA dissection and later developed recurrent distal dissection.

Twenty of the 53 patients with LDS (38%) had not yet required aortic surgery and were managed medically, constituting the non-aortic surgery group. Their maximum aortic diameter was 3.7 cm (Table 1). One patient in this cohort initially exhibited aortic root enlargement on yearly imaging and underwent an elective root reimplantation. For

TABLE 1. Patient demographics, comorbidities, imaging findings, and disease characteristics of 53 patients with Loeys-Dietz syndrome

Variable	Total (N = 53)	Aortic surgery (N = 33)	Non-aortic surgery (N = 20)
	No. of patients (%) or mean $\pm$ SD	No. of patients (%) or mean $\pm$ SD	No. of patients (%) or mean $\pm$ SD
Age (y)	36 (24)	39 (15)	23 (26)
Body mass index (kg/m ²)	24 (5)	25 (4)	23 (7)
Female	20 (38)	8 (24)	12 (60)
Mutation			
<i>TGFBR1</i>	8 (15)	6 (18)	2 (10)
<i>TGFBR2</i>	28 (53)	16 (48)	12 (60)
<i>SMAD3</i>	13 (25)	9 (27)	4 (20)
<i>TGFB2</i>	3 (6)	1 (3)	2 (10)
Unknown*	1 (2)	1 (3)	0 (0)
Family history of LDS	20 (38)	9 (28)	11 (55)
Family history of aortic pathology	35 (66)	23 (70)	12 (60)
Family history of undiagnosed CTD	24 (45)	14 (42)	0 (50)
Acute type I dissection	5 (9)	5 (15)	0 (0)
Acute type II dissection	1 (2)	1 (3)	0 (0)
Chronic type II dissection	1 (2)	1 (3)	0 (0)
Acute type III dissection	7 (13)	7 (21)	0 (0)
Chronic type III dissection	1 (2)	1 (3)	0 (0)
Hypertension	18 (34)	15 (45)	3 (15)
Cerebral vascular accident	6 (11)	5 (15)	1 (5)
Diabetes	1 (2)	1 (3)	0 (0)
COPD	7 (13)	4 (12)	3 (15)
Cancer	3 (6)	2 (6)	1 (5)
Dyslipidemia	7 (13)	6 (18)	1 (5)
Alcohol abuse	1 (2)	1 (3)	0 (0)
ASD	2 (4)	1 (3)	1 (5)
Bicuspid aortic valve	4 (8)	2 (6)	2 (10)
Endocarditis	1 (2)	1 (3)	0 (0)
Heart failure	3 (6)	3 (9)	0 (0)
NYHA class II	1 (2)	1 (3)	0 (0)
LVEF (%)	59 $\pm$ 5	58 $\pm$ 5	61 $\pm$ 5
Maximum aortic diameter (cm)†	3.7 (3.3-4.4)	4.3 (3.9-4.6)	3.4 (2.9-3.7)

TGFBR1, Transforming growth factor β receptor-1; *TGFBR2*, transforming growth factor β receptor-2; *SMAD3*, mothers against decapentaplegic homolog 3; *TGFB2*, transforming growth factor β 2 ligand gene; *LDS*, Loeys-Dietz syndrome; *CTD*, connective tissue disorder; *COPD*, chronic obstructive pulmonary disease; *ASD*, atrial septal defect; *NYHA*, New York Heart Association; *LVEF*, left ventricular ejection fraction. *This patient had confirmed LDS based on genetic testing at another institution, but details on the mutation are not available. †Median (Q1-Q3).

the analysis, this patient is categorized in the aortic surgery group. Patient characteristics and comorbidities are listed in Table 1.

Operative Details

The 33 patients in the aortic surgery group underwent 58 aortic operations (Table 2). Six patients (20%) had previous sternotomies for acute type I dissection repair (n = 3), 1 had acute type II dissection repair, 1 had aortic valve replacement, and 1 had mitral valve replacement.

Early Outcomes

Operative mortality. There were no operative deaths in patients undergoing elective surgery. There were 2 urgent or emergency surgery deaths (2/33; 6%). The first patient underwent an urgent extent-II thoracoabdominal aneurysm repair. Postoperatively, she developed infarcts in left middle cerebral artery distribution followed by hemorrhagic conversion, brain-stem herniation, and death. The second patient underwent an emergency aortic arch replacement with an elephant trunk procedure for a contained rupture

TABLE 2. Operative details of the aortic operation in 33 patients with Loeys-Dietz syndrome undergoing surgical repair

Variable	No. (% of 33)
Type of operation*	
Valve-sparing root reimplantation	19 (58)
Composite valve-graft root (mechanical)	4 (12)
Composite valve-graft root (biologic)	2 (6)
Allograft root replacement	1 (3)
Total arch replacement with ET	6 (18)
Total arch replacement	1 (3)
Extent IV open TAAA repair	1 (3)
Thoracic endovascular aortic repair	2 (6)
Concomitant procedures	
Mechanical mitral valve replacement	1 (3)
Coronary artery bypass grafting	2 (6)
Atrial septal aneurysm repair	1 (3)
Mitral valve repair	1 (3)
Septal myectomy	1 (3)
Urgency of aortic repair	
Elective	25 (76)
Urgent	4 (12)
Emergency	4 (12)
Symptomatic at presentation	7 (21)
Operative data, mean $\pm$ SD; median (Q1-Q3)†	
Operative time (min)	313 $\pm$ 127; 241 (216-407)
Cardiopulmonary bypass time (min)	129 $\pm$ 55; 128 (102-162)
Aortic clamp time (min)	108 $\pm$ 49; 99 (81-131)
Circulatory arrest time (min)	7 $\pm$ 22; 0
Intraoperative RBC (units)	1 $\pm$ 3; 0
Intraoperative FFP (units)	1 $\pm$ 3; 0 (0-1.5)
Intraoperative platelets (units)	0.6 $\pm$ 1.5; 0 (0-0.5)
Intraoperative cryoprecipitate (units)	0.5 $\pm$ 1.5; 0

ET, Elephant trunk; IV, intravenous; TAAA, thoracoabdominal aortic aneurysm; RBC, red blood cells; FFP, fresh frozen plasma. *There was more than 1 aortic operation with multicomponent aortic repair performed at the time of index aortic surgery in 3 patients. †Operative data are available for 31 patients undergoing their index operation at our institution.

of the distal ascending aorta. Postoperatively, she developed stroke in the right basal ganglia with hemorrhagic transformation and did not survive (Table E1).

Postoperative adverse events. Three postoperative strokes occurred (9%). Two patients died, as described in the preceding section. The third patient developed acute pontine infarct after a valve-sparing root reimplantation. He underwent an immediate mechanical thrombectomy of basilar artery occlusion and completely recovered. He was last seen 42 months postoperatively and was doing well.

No patients experienced myocardial infarction, heart block requiring a pacemaker, renal failure requiring dialysis, tracheotomy, hepatic dysfunction, deep venous thrombosis or pulmonary embolism, superficial or deep sternal wound infection, or sepsis. A low prevalence of other postoperative adverse outcomes was observed (Table 3).

Blood pressure control. Blood pressure control in our series was excellent (goal 130/80 mm Hg). Mean blood

TABLE 3. Operative outcomes of 33 patients with Loeys-Dietz syndrome undergoing surgical repair

Outcome	No. (% of 33)
Stroke	3 (9)
Respiratory failure	3 (9)
Atrial fibrillation	3 (9)
Ventricular tachycardia	1 (3)
Reoperation for bleeding	3 (9)
Postoperative RBC transfusion	5 (15)
Postoperative FFP transfusion	4 (12)
Postoperative platelet transfusion	4 (12)
Postoperative cryoprecipitate transfusion	4 (12)
ICU length of stay, median hours (Q1-Q3)	27 (24-68)
Hospital length of stay, median days (Q1-Q3)	8 (6-11)
Hospital death	2 (6)
Operative death	2 (6)
Readmission	8 (24)

RBC, Red blood cell; FFP, fresh frozen plasma; ICU, intensive care unit.

pressure of the entire cohort was $118 \pm 16/68 \pm 10$ mm Hg. Of 53 patients, 30 (57%) were taking β -adrenergic-blocking drugs, 5 (9%) were taking angiotensin-converting enzyme inhibitors, 31 (58%) were taking angiotensin receptor blockers, 4 (8%) were taking calcium channel blockers, and 5 (9%) were taking diuretics.

LDS and Cardiomyopathy

One patient in our series with a novel *TGFBR1* mutation developed severe cardiomyopathy and underwent total aortic replacement and orthotopic heart transplantation 14 months after an initial type I aortic dissection.² He is doing well 8 years after his last aortic surgery. It is possible that the *TGFBR1* mutation led to the microvascular dysplasia of his coronary arteries and cardiomyopathy, as noted on the pathology evaluation of the explanted heart. This association is yet to be determined.

Late Outcomes

Aorta-related reoperations. Twenty-two of 33 patients (67%) in our aortic surgery group required no aortic reoperation. Indications for surgery were prophylactic aortic repair for an enlarging aortic root and ascending aortic aneurysm in 20 patients (91%) and acute type I aortic dissection in 2 patients (9%).

Valve-sparing root replacement was the prophylactic aortic operation in 95% (19/20) of these patients. Seventeen (85%) of these procedures were LGS-modified valve-sparing root reimplantations performed at our institution. Two patients (10%) had valve-sparing root reimplantations performed at outside institutions. One patient with a bicuspid aortic valve (5%) required a mechanical composite valve-graft root replacement.

TABLE 4. Indications for the 36 aortic operations in 11 patients with Loeys-Dietz requiring multiple aortic reoperations*

Indication for aortic operation	No. of patients
Acute type I aortic dissection	3
Acute type II aortic dissection	2
Acute type III dissections with rupture/contained rupture	3
Acute type III dissection with Kommerell diverticulum	1
Chronic type III aortic dissection with aneurysm	1
Enlarging aortic root aneurysm with aortic insufficiency	7
Aortic root pseudoaneurysm with allograft degeneration	1
Prosthetic aortic valve endocarditis/failure	2
Expanding aortic arch aneurysm	5
Rupture of aortic arch aneurysm with residual dissection	1
Expanding DTAA with residual dissection	4
TAAA with residual dissection	8
Infrarenal AAA	2

DTAA, Descending thoracic aortic aneurysm; TAAA, thoracoabdominal aortic aneurysm; AAA, abdominal aortic aneurysm. *Four patients had more than 1 indication for aortic reoperation.

Composite valve-graft root replacement was performed on both patients with acute type I aortic dissection. Two patients (6%) required concomitant total aortic arch replacement, 1 of whom had acute type I aortic dissection. Aortic valve repair at the time of root reimplantation was performed in 2 patients (6%). There have been no operative deaths in this subgroup.

Late outcomes of modified root reimplantation were excellent. Among the 19 patients who underwent reimplantation, there were no aortic valve-related reoperations, thromboembolism, endocarditis, or late aortic dissections. No patients developed coronary artery button aneurysms, anastomotic dehiscence, or arch aneurysm requiring reoperation.

Multiple aortic operations. Multiple aortic operations were performed on 11 of 33 patients (33%). In this subgroup, 9 of the 11 patients (82%) had experienced acute aortic dissections. Overall, these patients underwent 36 aortic operations, with a mean of 3.3 aortic operations per person (Table 4). The initial aortic operation was performed at another institution in 7 patients (64%). They were subsequently referred to our Aorta Center for a second or third aortic reoperation (Table E1).

Most reoperations were for distal aortic degeneration and aneurysm formation. Total arch replacement with elephant trunk procedures were performed on 64% (7/11) of the patients requiring aortic reoperations. Overall, 18% (6/33) of patients in the aortic surgery group had total aortic replacement. All these patients had prior aortic dissection, and their arch replacements were performed at our institution.

Aortic root reoperations. Four patients (12%) required reoperations on the aortic root. Two of these reoperations

were for root and arch degeneration after a simple supracoronary ascending aortic replacement for type I aortic dissection. The remaining 2 root reoperations were for prosthetic aortic valve endocarditis and late structural valve deterioration of an allograft root. Estimated freedom from aorta-related reoperations among dissection and nondissection patients at 1, 5, and 10 years was 45%, 27%, and 14% versus 100%, 100%, and 86%, respectively ($P < .0001$; Figure 2).

There were 3 deaths, all in aortic surgery group. Among the 31 of 33 surviving patients, there was 1 late death, caused by a ruptured descending thoracic aortic aneurysm in a patient who had aortic root reimplantation performed at another institution 10 years previously. He was followed at our institution for a stable 3.8-cm descending thoracic aneurysm. He presented with back pain. On CTA he was found to have an expanding (5.7-cm) descending thoracic aortic aneurysm with focal dissection. He was immediately transferred to our institution, but died from aortic rupture shortly after transfer. He did not regain any vital signs despite substantial resuscitation efforts and hemodynamic support.

Overall, 33 patients in the aortic surgery cohort underwent a total of 58 aortic and 81 cardiovascular operations (Table 5). Kaplan-Meier survival of the aortic surgery group was 89% at 10 years (number at risk = 8 at 10 years; Figure 3). Their median follow-up was 5.2 years. Median follow-up for the non-aortic surgery group was 8.4 years. There were no deaths in this group.

Spontaneous fractures and primary inguinal, umbilical, postsurgical, and recurrent ventral hernias occur frequently in patients with LDS. In our series, 53 orthopedic and general surgical procedures were performed in our full cohort (Table 6). An intracranial aneurysm was identified in 20% (9/44) of our study patients who underwent CTA or MRI/MRA of the brain. Currently, all patients with LDS undergo an initial intracranial aneurysm screening as part of their cardiovascular surveillance at our institution.

Twenty patients (38%) in our series were first-degree relatives (parents, siblings, and offspring; 8 probands and 12 family members [non-probands]). Of these, 10 patients required surgical intervention: 63% of probands (5/8) and 42% of non-probands (5/12). One proband underwent an emergency aortic repair. The remaining 10 patients (4 probands, 6 non-probands) are being treated medically, with ongoing surveillance. The aortopathy was more aggressive in probands than in non-probands (Table E2).

DISCUSSION

Since the initial description of LDS,³ there has been significant progress in understanding the biology, phenotype, and natural history of this disease.¹⁻⁹ Recently, it has been suggested that LDS be divided into 5 subtypes based on the presence of aortic aneurysm or dissection in combination with a gene mutation in *TGFBR1* (LDS 1),

FIGURE 2. Freedom from aortic reoperation after initial aortic surgery in patients with and without a history of aortic dissection.

TGFBR2 (LDS 2), *SMAD3* (LDS 3), *TGFB2* (LDS 4), and *TGFB3* (LDS 5).^{9,10} Previous studies demonstrated that patients with LDS types 1 and 2 are at greater risk of aortic dissection and rupture at an earlier age and smaller aortic diameter.^{3,4,16} In our series, among 11 patients who developed aortic dissections, 7 (64%) had *TGFBR2* mutation, 3 (27%) had *SMAD3* mutation, and 1 (9%) had *TGFBR1* mutation. None of the 3 patients with *TGFB2* mutation exhibited aortic dissection or rupture on presentation. This is consistent with previous reports, suggesting an aggressive nature of aortopathy in patients with *TGFBR2* (LDS 2) mutation and perhaps a less aggressive phenotype in *TGFB2* (LDS 4) patients. There is evidence that not all subtypes of LDS should be treated equally. In fact, patients with mutations in *TGFB2* (LDS 4) might not need surgical intervention as early.¹⁷ The decision to perform a prophylactic aortic repair in patients with LDS has been driven primarily by aortic diameter, but other considerations include rate of aortic growth, aortic valve function, phenotype, and family history.

Guidelines for medical management, clinical and radiologic surveillance, and the threshold for surgery have been suggested for these patients.¹¹ Initially, 4.2 cm was recommended as the threshold for performing elective operations, based on little information from a practice that has concentrated on pediatric patients.⁴ However, because of the malignant natural history of the vasculopathy and established safety of prophylactic root replacement at experienced centers, recent recommendations suggest performing surgical repair of the aortic root at diameters of approximately 4.0 cm.⁹ Another large, multicenter retrospective study recommended aortic surgery at 4.5 cm unless other factors suggest a more severe presentation.¹⁸

Considering the 1 late death in our study and older reports of “Marfanoid” patients developing DeBakey type III dissection, earlier intervention on the descending aorta may also be warranted for many patients with LDS.^{19,20}

Some groups have reported their surgical experience with LDS.^{16,21-23} Recently, Patel et al. published their series of patients with LDS who underwent cardiovascular surgery at Johns Hopkins, with excellent outcomes.¹⁷ Their growing experience confirmed the aggressive nature of aortopathy, with a higher predisposition toward aortic catastrophe at a young age and smaller aortic diameter. A few significant differences exist between our series and their report. Our series represents the experience at most cardioaortic centers treating a largely adult population. Almost half of the patients (48%) in their series were children (age < 18 years), compared with 12% in ours, and mean age at index operation was 25 versus 39 years, respectively. Moreover, our series has a 33% prevalence of aortic dissection compared with 8% in the largely elective practice of Patel et al.¹⁷ Aortic reintervention remains high in these patients, 36% in our cohort versus 25% in theirs, with most reinterventions due to distal aortic or arch degenerations.

Aorta-Related Reoperations

Prevalence of aorta-related reoperation is higher among patients who had initial aortic operation for an acute type I dissection. In our series, 82% (9/11) of patients who underwent multiple aortic interventions had a history of acute aortic dissection. We previously demonstrated this high risk for late and multiple aortic reoperations in other patients with connective tissue disorders.²⁴ In this report, 18% (6/33) of patients underwent total aortic replacement in a staged fashion, and all had a history of aortic dissection. Iba et al.²² reported a

TABLE 5. Operative details of all 58 aortic and 81 cardiovascular procedures performed on 33 patients with Loeys-Dietz syndrome in the aortic surgery group

Total aortic/cardiovascular procedures	No. of patients
Root operations (combinations)	33
Valve-sparing root reimplantation + ascending/hemiarch	11
Valve-sparing root reimplantation + ascending + total arch replacement	2
Valve-sparing root reimplantation + aortic valve repair + ascending	5
Valve-sparing root reimplantation + mitral valve/atrial septal aneurysm repair	2
CVG (mechanical) + ascending/hemiarch	5
CVG (mechanical) + ascending + total arch	2
CVG (mechanical) + ascending + MVR	1
CVG (biologic) + ascending + total arch + ET	1
CVG (biologic) + ascending + CABG	2
Allograft root + ascending/hemiarch	1
Allograft root + CABG	1
Ascending aortic operations (combinations)	6
Ascending/hemiarch	1
Ascending/hemiarch + aortic valve resuspension	2
Ascending + total arch + ET	3
Isolated aortic arch operations	1
Arch replacement	1
Descending thoracic aortic operations	8
Open descending repair	3
TEVAR	5
Thoracoabdominal aortic operations	7
Open TAAA repair	7
Infrarenal abdominal aortic operations	3
Open infrarenal repair	2
EVAR infrarenal aortobiliac repair	1
Total aortic operations	58
Non-aortic cardiac operations	3
Mechanical aortic valve replacement	1
Bioprosthetic mitral valve replacement	1
Orthotopic heart transplant	1
Vascular operations	20
Open vascular repair	2
Endovascular repair of peripheral vascular aneurysm	4
Extra-anatomic bypass	7
Subclavian artery/branch vessels embolization	6
Mechanical thrombectomy	1

CVG, Composite valve-graft replacement; MVR, mitral valve repair or replacement; ET, elephant trunk; CABG, coronary artery bypass grafting; TEVAR, thoracic endovascular aortic repair; TAAA, thoracoabdominal aortic aneurysm; EVAR, endovascular aortic repair.

significantly higher prevalence of total aortic replacement (40%) in patients with LDS after aortic dissection.

Our current practice is not to perform routine arch replacement at the time of an elective aortic root and hemiarch replacement. In our aortic surgery cohort, no patient who

underwent an elective aortic root operation developed aortic arch degeneration requiring reoperation. All are being followed with regular imaging. Our data suggest that the aggressive natural history of LDS may be modified with a timely prophylactic aortic operation.

Two of the 4 root and all arch reoperations in our series were for patients who initially presented with aortic dissection. Given the significantly high prevalence of aortic reintervention in LDS patients presenting with aortic dissection, it is justifiable to perform total arch or root replacement, or both, at the initial type I dissection repair, particularly if the patient is stable and necessary surgical expertise is available.

In our Aorta Center and the Marfan Syndrome and Connective Tissue Disorder Clinic, we stress the importance of lifelong care for these patients. Patients with a prior aortic dissection are followed more frequently.²⁴ In our previous report of prophylactic modified valve-sparing root repair in 178 patients with connective tissue disorders, we demonstrated safety with no operative deaths, and effectiveness with 92% freedom from aortic valve reoperation at 6 years.²⁵ We emphasize early prophylactic root replacement for LDS patients to avoid catastrophic vascular complications. Our modified valve-sparing root reimplantation procedure is our preferred option in these patients.¹² However, not every patient is a good candidate. Patients with significant cusp degeneration, such as calcification or multiple large fenestrations, may be better treated with composite valve-graft root replacement.

Congenital cardiac anomalies, such as mitral valve prolapse, atrial septal defect, or patent ductus arteriosus, occur frequently in patients with LDS. In our series, 2 patients underwent concomitant mitral valve surgery and root replacement; 1 patient had a concomitant atrial septal aneurysm repair. This association may be more common than previously appreciated for other connective tissue disorders as well.²⁶

Role of Endovascular Therapies in Patients With LDS

Connective tissue disorders are considered a relative contraindication for endovascular aortic repair because of the risk of progressive aortic dilatation or dissection at the landing zones. It has been our practice to use endovascular techniques as a complement to open repair for patients with connective tissue disorders and specific indications for surgery. In our series, 6 patients needed endovascular repair. Two had emergency TEVAR for malperfusion, and 2 underwent intervention for an intercostal patch aneurysm and iliac artery aneurysm after previous open TAAA repair. The last 2 patients underwent TEVAR for urgent second-stage elephant trunk and because of a hostile abdomen from recent spontaneous colonic perforations.²⁷ One patient will likely require an open TAAA repair.^{24,28}

LDS is a lifelong disease, and endovascular therapies are important adjuncts to open repair, especially for aortic dissections, ruptures, and peripheral vascular aneurysms. As reported by others,²⁹ it is reasonable to perform an endovascular repair

FIGURE 3. Kaplan-Meier survival curve for the 33 patients in the aortic surgery cohort with Loeys-Dietz syndrome.

of a localized segment of aorta when both the proximal and distal landing zones lie within a surgical graft.

Noncardiovascular Manifestations

A recent study reported that 60% of patients with LDS had low bone mineral density in the spine, hip, or femoral neck. There is a 50% risk of developing fractures by 14 years of age in patients with LDS types 1 and 2.³⁰ Other life-threatening conditions include splenic and bowel rupture requiring surgery.⁴ Our experience suggests that patients with LDS should be counseled about the high occurrence of noncardiovascular complications and risk of fractures.

CONCLUSIONS

Loeys-Dietz syndrome carries a malignant prognosis, with early presentation of dissection and rapid progression of

TABLE 6. Details of orthopedic and general surgical procedures on 53 patients with Loeys-Dietz syndrome

Detail	Total (N = 53)	Non-aortic surgery cohort (N = 20)	Aortic surgery cohort (N = 33)
Orthopedic and general surgical operations	53	26	27
Orthopedic operations	22	10	12
Total knee replacement	2	0	2
Total hip replacement	2	0	2
Total shoulder replacement	2	2	0
Arthroscopy	6	2	4
Pectus excavatum repair	6	3	3
Rotator cuff repair	2	1	1
Spinal fusion	2	2	0
General surgical operations	31	15	16
Inguinal hernia repairs	14	7	7
Unspecified hernia repair	10	4	6
Total or partial colectomy	6	3	3
Small bowel resection	1	1	0

aneurysmal dilatation if not treated before dissection occurs. A multidisciplinary approach and close collaboration between cardiologists, cardiovascular surgeons, and geneticists is essential for early recognition, close surveillance, and timely prophylactic surgery on these patients to prevent catastrophic complications. Physicians should consider the syndrome when patients exhibit aortic dilatation at a young age and variable connective tissue findings appear “Marfanoid” and may overlap with Marfan syndrome. Early referral to a high-volume center with expertise in the care of patients with aortic disease may result in more favorable outcomes.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/18May01/28ABC%202.Aortic%20Endovascular/S86%20-%20Part%202/S86_3_webcast_043552738.mp4.

Conflict of Interest Statement

M.A. is a consultant for Biom’Up and a member of the Clinical Events Committee; C.M.R. is a consultant for Ambry Genetics and My Gene Counsel; E.E.R., is a speaker and consultant for Medtronic, St. Jude Medical, LivaNova, Cook Medical, Bolton Medical, and Terumo; L.G.S. receives royalties for inventions or discoveries commercialized through Posthorax GmbH and is an unpaid member of the Executive Committee for PARTNER trials I and II and the COMMENCE trial, which are sponsored by Edwards Lifesciences. All other authors have nothing to disclose with regard to commercial support.

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Key Words: aorta surgery, connective tissue disorder, Loeys-Dietz syndrome, Marfan

Discussion

Dr Duke Cameron (Baltimore, Md).

Mr Cikach, thank you for an excellent presentation summarizing your institution's experience with Loeys-Dietz syndrome. Because the disease is rare and was only recognized 13 years ago, it is clear there is still a lot to learn about its features, the various subtypes, the natural history, and its response to our interventions. With the discovery of any new disease, there is a tendency for the most severe phenotype to be described first, which can lead to an exaggerated view of its aggressiveness. In the case of Loeys-Dietz syndrome, those initial suspicions about severity have been borne out, at least for certain subtypes.

I agree very much with all of your major findings and recommendations, which are that prophylactic surgery is low risk; valve-sparing procedures are usually appropriate and successful; reinterventions are common, especially in the setting of dissection; these patients need very close surveillance; and finally, that endovascular interventions really have a limited role. I have 2 very simple, straightforward questions for you.

You point out that you routinely screen for intracranial aneurysms and have identified them in 20% of your patients. What do you do with that information? Have you intervened on any patients with aneurysm and what are the criteria for intervention?

Mr Cikach (Cleveland, Ohio). Most of the intracranial aneurysms in our series were quite small. We did refer to neurosurgery for those aneurysms, but I think a very low rate of those were actually intervened upon.

Dr Cameron. Very good. The second question concerns routine arch replacement at the time of root surgery. You do not recommend concomitant arch replacement because in your experience

the arch has very infrequently required late intervention unless a dissection was present initially. You also rightly pointed out that your series and our old series from Hopkins differed in that your patients were much older; your mean age was 39 years, ours was 25 years and included some much, much younger children. I just want to point out that in our younger patients the arch did dilate in the absence of dissection within a few years of the root replacement and required intervention while the patient was in early adolescence. In fact, the original patient with Loeys-Dietz syndrome—the indexed patient—needed a root replacement, then needed a late arch replacement, and then died from a rupture of a very proximal left subclavian aneurysm. My point is that in very young patients it may be that a more aggressive approach to the arch is indicated. I think that's the only distinction we would make from your recommendations; that is, that young patients need a little more aggressive attention to the arch. Thank you very much for an excellent presentation.

Mr Cikach. Thank you. I think that's a great point about the arch in young patients. Once we collect more data on more patients, we will start to get a little more granular with what we can pull out of that data and understand which patients would be best served by prophylactic root and arch procedures and in which patients can we let the arch go. As we get more registries—and more patients in these registries—we can identify which patients are at risk of late arch aneurysms.

Dr Lars G. Svensson (Cleveland, Ohio). Duke, you bring up a very important point about what to do with the arch. We tended to be a bit conservative, but I think you are right that we are going to have to do more for the arch in these patients, because as you know, their greater vessels are often aneurysmal, too.

A couple of patients with aortic dissection required multiple subclavian and innominate procedures later, after individual bypasses were performed. There is 1 patient I can think of offhand who required reimplantation. Everything was fine, but later a subclavian artery aneurysm developed.

You bring up another very important point. The spectrum of disease in these patients—and these were all genetically identified—is much broader than in Marfan syndrome. You have experience with a younger pediatric population that we largely haven't seen. I have seen a few teenagers but not many. What's interesting is that we have also had patients aged ≥ 60 years with Loeys-Dietz syndrome and also aneurysms 5.5 to 6 cm in size. A patient with genetically identified Loeys-Dietz syndrome on whom I worked at the beginning of last week was aged 61 years, had a 5.5-cm aneurysm, and yet never dissected.

We don't know how to better identify these patients. It looks like some of the genetic mutations are more prone to disease and require earlier intervention. You have heard me

say this before: When Dianna Milewicz and I were asked to put size into the guidelines, we looked at your recommendation and also thought about the presenting older patients. We basically punted and said, well, 4.2 cm sounds reasonable and hopefully the research will show if this is the right number or not. Our data show you can safely do it at 4.2 to 4.3 cm. It doesn't show what would have happened if we had been more conservative, obviously.

Dr Cameron. I agree 100% and it is such an important point. The spectrum of this disease is much broader than we thought, and it isn't going to sort out exactly by genotypic subtypes. There are lots of other factors. We have to get a lot smarter about knowing when to intervene.

Dr Himanshu Patel (Ann Arbor, Mich). You describe a number of patients who have had aneurysms. Has anybody had a spontaneous dissection within the arch?

Mr Cikach. Yes, and type B dissection is reported.

Dr Patel. Type B is different, but I am curious: With the recommendation to perhaps do a more aggressive arch resection, would that be done to prevent dissection essentially within that area?

Mr Cikach. I have seen 2 patients who underwent a valve-sparing root procedure and over 4 or 5 years dilated and then dissected. I know Bavaria has experience with this as well, because they published a case report a few years ago and recommended prophylactic hemiarch in these young patients.

Regarding intracranial aneurysms, our practice is to get a baseline on everyone, then follow-up with them about every 2 years. We have a pretty large Loeys-Dietz syndrome series. For a while we thought, well, maybe this is not useful. But we have had 2 patients within the past 2 years who have developed intracranial aneurysms under surveillance, and 1 had a stroke from it, and they were young patients. So there is more to learn.

Dr Patel. Do you scan their head every 2 years as well?

Mr Cikach. Magnetic resonance angiogram, not computed tomography.

Dr Svensson. As far as our patients and intracranial aneurysms, I have sort of taken the approach that we should keep a close eye on patients during the perioperative period and just be aware that if they do bleed, we know it.

Dr Eric Roselli (Cleveland, Ohio).

And another thing I think we are going to learn about the spectrum of this syndrome is the importance of tortuosity. We had 1 young patient on whom Lars and I, and Roy Greenberg, and Bruce Lytle, and everybody who has ever operated on an aorta operated on; she presented when she was 12 years old with a

dissection. We replaced her aorta, we thought things were looking pretty good, and then she died in her late 20s after we had replaced everything we thought could be aneurysmal; she ruptured a medium-size vessel that happened to be very tortuous.

So, again, with people who present at a younger age, not only should we consider being more aggressive about the arch and the aorta as Duke suggested, but we should also be more aggressive in our imaging surveillance.

Dr Svensson. Eric, you touched on an important point that Duke was also bringing up. The greater vessels in these patients are at a much greater risk of developing

aneurysms than in patients with Marfan syndrome. If you are going to do individual bypasses to the greater vessels, make sure your anastomosis is absolutely waterproof before you progress, because it is going to be difficult to get back to those very fragile tissues. It is like the Ehlers-Danlos patient: Use 5-0 or 6-0 with small pledgets of interrupted sutures on the back wall, because you are not going to be able to go back in. If you try, you risk everything falling apart.

Dr Roselli. Great. Thank you. If anyone wants to speak to Dr Aftab afterward, I am going to offer him to be available. Great job, Frank.

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TABLE E1. Operative details and indications for the 36 aortic operations in 11 patients requiring multiple aortic reoperations

Patient no.	Age at first aortic operation (y)	Age at index operation (y)	Gene mutation	Initial aortic operation (index operation indicated in bold)	Aortic reoperations (index operation indicated in bold)	Operative indications	Additional vascular/cardiac interventions	Duration (1st to last aortic surgery, y)	Total aortic operations	Patient status
1	61	68	<i>SMAD3</i>	AsAR + TAR	TEVAR Urgent redo extent II TAAA repair	Acute AD (I) DTAA Residual enlarging TAAA		8	3	Dead
2	31	39	<i>SMAD3</i>	AsAR + right coronary sinus reconstruction + AV resuspension	VSR , repair of atrial septal aneurysm TAR	AD (II) ARA + severe AI + PFO + atrial septal aneurysm Expanding ArcA		13	3	Alive
3	36	37	<i>TGFBR2</i>	M-CVG	Emergency AsAR + TAR + ET	AD (I) + AI ArcA + DTAA		1	2	Dead
4	29	29	<i>TGFBR2</i>	M-CVG, Cabrol shunt from aorta to right atrium	Infrarenal AAA repair Open DTA repair TEVAR (mid-DTA to celiac axis) TAAA repair Allograft ARR + AsAR + HAR	ARA + AI Acute AD (III) + AAA Enlarging DTAA Enlarging distal DTAA Extent II TAAA Aortic valve endocarditis	After index operation: Stenting of SMA due to occlusion from dissection flap After last aortic operation: VA fistula embolization	14	6	Alive
5	52	52	<i>TGFBR2</i>	B-CVG + AsAR + TAR + ET	Extent II TAAA repair EVAR	Chronic AD (II) + ARA + AsAA Chronic AD (III) type-III + extent II TAAA Distal AAA + bilateral iliac aneurysm	After last aortic intervention: Left SCvA aneurysm, CA-SCvA bypass + VA reimplantation; embolization of SCvA + TCT	2	3	Alive
6	44	45	<i>TGFBR1</i>	AsAR + AV resuspension	M-CVG + CABG + AsAA + TAR + ET OHT TAAA repair	Acute AD (I) Enlarging ARA + ArcA + DTAA DCMP Extent II TAAA	Before second-stage ET completion: Left CA-SCvA bypass	1	4	Alive
7	12	12	<i>TGFBR2</i>	Right CA to SCvA bypass, ligation of aberrant right SCvA + ASAR + TAR + ET	M-CVG Extent II TAAA repair	Acute AD (IIIA) + bovine arch, aberrant right SCvA behind trachea and esophagus + DTAA ARA + AI Acute AD (IIIB) + extent II TAAA	After second aortic operation: Bilateral CA-AxA bypasses + VA reimplantation for SCvA and VA aneurysms;	6	3	Alive

(Continued)

TABLE E1. Continued

Patient no.	Age at first aortic operation (y)	Age at index operation (y)	Gene mutation	Initial aortic operation (index operation indicated in bold)	Aortic reoperations (index operation indicated in bold)	Operative indications	Additional vascular/cardiac interventions	Duration (1st to last aortic surgery, y)	Total aortic operations	Patient status
8	35	35	<i>TGFBR2</i>	Emergency TEVAR covering left SCvA	Reimplantation + AsAR, TAR + ET Second-stage ET + open DTA repair Redo extent II TAAA repair	Acute AD (III) with malperfusion ARA + residual dissection in DTA Extensive dissection in DTA Extent II TAAA expansion of visceral segment	embolization of bilateral ITA and SCvA Prior to index operation: Right to left CA and left CA to left SCvA bypass After index operation: False lumen embolization of left SCvA	2	4	Alive
9	40	47	<i>TGFBR2</i>	Open AAA repair	Allograft ARR + CABG Extent II TAAA repair Redo B-CVG, AsAR + CABG TEVAR	AAA ARA + AI + CAD TAAA Aortic root PSA + severe AI + CAD DTAA	After second aortic operation: Open repair of left common femoral artery PSA After fourth aortic operation: Right CEA	18	5	Alive
10	31	42	Unknown*	B-CVG + AsAR + TAR	TEVAR from proximal DTA celiac artery	ARA + AsAA previous stroke due to warfarin noncompliance DTAA	Prior to first aortic operation: Mechanical AVR for severe AI	11	2	Alive
11	45	46	<i>TGFBR2</i> and <i>COL3A1</i>	Emergency DTA repair	AsAR + TAR + ET	Ruptured AD (III) AsAA + ArcA + DTA PSA + TAAA	After index operation: Endovascular repair of left SCvA aneurysm	0.6	2	Alive

SMAD3, Mothers against decapentaplegic homolog 3; *AsAR*, ascending aortic replacement; *TAR*, total arch replacement; *TEVAR*, thoracic endovascular aortic repair; *TAAA*, thoracoabdominal aortic aneurysm; *AD (I)*, aortic dissection type-I; *DTAA*, descending thoracic aortic aneurysm; *AV*, aortic valve; *VSRR*, valve-sparing root repair; *TAR*, total arch replacement; *AD (II)*, aortic dissection type-II; *ARA*, aortic root aneurysm; *AI*, aortic insufficiency; *PFO*, patent foramen ovale; *ArcA*, arch aneurysm; *TGFBR2*, transforming growth factor β receptor-2; *M-CVG*, mechanical composite valve-graft replacement; *ET*, elephant trunk; *AAA*, abdominal aortic aneurysm; *DTA*, descending thoracic aorta; *ARR*, aortic root replacement; *AsAA*, ascending aortic aneurysm; *HAR*, hemiarch replacement; *AD (III)*, aortic dissection type-III; *SMA*, superior mesenteric artery; *VA*, vertebral artery; *B-CVG*, bioprosthetic composite valve-graft replacement; *EVAR*, endovascular aortic repair; *SCvA*, subclavian artery; *CA*, carotid artery; *TCT*, thyrocervical trunk; *OHT*, orthotopic heart transplantation; *CABG*, coronary artery bypass grafting; *DCMP*, dilated cardiomyopathy; *AD (IIIA)*, aortic dissection type-IIIA; *AD (IIIB)*, aortic dissection type-IIIB; *AxA*, axillary artery; *ITA*, internal thoracic artery; *PSA*, pseudoaneurysm; *CAD*, coronary artery disease; *CEA*, carotid endarterectomy; *AVR*, aortic valve replacement. *LDS confirmed with genetic testing at outside hospital.

TABLE E2. Clinical and genetic characteristics of 20 related patients from 12 families (8 probands and 12 non-probands) with Loeys-Dietz syndrome

Patient no.	Family no.	Patient no. in family	Age at index operation or 1st presentation	Sex	Mutation	Proband vs Non-Proband	Status	Operative details (index operation indicated in bold)	Operative indications
1	1	1	29	Male	TGFBR2	Proband	Surgery	CVG (mechanical) Infrarenal AAA repair Open DTAA repair TEVAR (mid-descending aorta to celiac axis) Extent II TAAA repair Redo allograft aortic root replacement Vascular procedures: SMA stenting Vertebral artery fistula embolization	Aortic root aneurysm, severe AI Type-III dissection – enlarging AAA Enlarging DTAA Enlarging distal DTAA Enlarging extent II TAAA aneurysm Aortic valve endocarditis Static SMA obstruction from dissection flap Vertebral artery to paravertebral venous plexus fistula
2	1	2	12	Male	TGFBR2	Non-proband	Surgery	Valve-sparing root reimplantation	Aortic root aneurysm
3	2	1	52	Male	TGFBR2	Proband	Surgery	CVG (biologic) + ascending + total arch replacement (bypasses to arch branches) with elephant trunk Extent II TAAA repair with elephant trunk completion (bypasses to intercostal, SMA, celiac, and bilateral renal arteries) EVAR for infrarenal AAA, stent grafting of right internal and external iliac arteries Vascular procedures since aortic intervention: Left carotid to brachial artery bypass; vertebral artery reimplantation	Chronic type-II dissection + new subacute type-III dissection Chronic type-III dissection Infrarenal AAA with residual dissection into the common iliac arteries Left subclavian artery aneurysm Subclavian artery branch vessels aneurysm

(Continued)

TABLE E2. Continued

Patient no.	Family no.	Patient no. in family	Age at index operation or 1st presentation	Sex	Mutation	Proband vs Non-Proband	Status	Operative details (index operation indicated in bold)	Operative indications
								Embolization of left subclavian, proximal axillary artery, and thyrocervical trunk	
4	2	2	51	Male	<i>TGFBR2</i>	Non-proband	Surgery	Valve-sparing root reimplantation	Aortic root aneurysm
5	2	3	23	Male	<i>TGFBR2</i>	Non-proband	Surgery	Valve-sparing root reimplantation + ascending + total arch replacement (bypasses to brachiocephalic and left common carotid arteries)	Aortic root aneurysm
6	2	4	18	Male	<i>TGFBR2</i>	Non-proband	Surgery	Valve-sparing root reimplantation + ascending + transverse hemiarch replacement	Expanding aortic root and ascending aortic aneurysm
7	3	1	28	Male	<i>TGFBR2</i>	Proband	Surgery	CVG (mechanical), mechanical mitral valve replacement, transverse hemiarch replacement Prior to index operation: Bioprosthetic mitral valve replacement Right common carotid to right vertebral artery bypass Stent grafting of left subclavian and axillary arteries, embolization of left vertebral artery Embolization of right vertebral artery	Aortic root and ascending aortic aneurysm + bioprosthetic mitral valve degeneration Severe mitral regurgitation Right vertebral artery aneurysm Left subclavian and vertebral artery aneurysms Right vertebral artery aneurysm
8	3	2	5	Male	<i>TGFBR2</i>	Non-proband	Surveillance	N/A	N/A
9	4	1	32	Male	<i>TGFB2</i>	Proband	Surgery	Valve-sparing root reimplantation	Expanding aortic root aneurysm

(Continued)

TABLE E2. Continued

Patient no.	Family no.	Patient no. in family	Age at index operation or 1st presentation	Sex	Mutation	Proband vs Non-Proband	Status	Operative details (index operation indicated in bold)	Operative indications
10	4	2	3	Female	<i>TGFB2</i>	Non-proband	Surveillance	N/A	N/A
11	5	1	47	Male	<i>TGFBR2</i>	Proband	Surgery	Open AAA repair Aortic root replacement with allograft, CABG × 1 (saphenous vein graft to right coronary artery) Extent II TAAA repair (bypasses to celiac, SMA, and bilateral renal arteries) Redo aortic root replacement with CVG (biological), CABG × 1 (saphenous vein graft to posterior descending artery) TEVAR Additional vascular procedures: Open repair of left common femoral artery pseudoaneurysm Right carotid endarterectomy	AAA Aortic root aneurysm, severe aortic insufficiency, coronary artery disease Extent II TAAA with enlarging visceral segment Enlarging aortic root pseudoaneurysm, severe aortic insufficiency, coronary artery disease Expanding DTAA Left common femoral artery pseudoaneurysm Right carotid artery stenosis
12	5	2	38	Female	<i>TGFBR2</i>	Non-proband	Surveillance	N/A	N/A
13	6	1	38	Female	<i>TGFBR2</i>	Proband	Surveillance	N/A	N/A
14	6	2	59	Male	<i>TGFBR2</i>	Non-proband	Surgery	Open AAA repair (at another institution)	AAA
15	6	3	6	Male	<i>TGFBR2</i>	Non-proband	Surveillance	N/A	N/A
16	6	4	2	Female	<i>TGFBR2</i>	Non-proband	Surveillance	N/A	N/A
17	7	1	10	Female	<i>TGFBR1</i>	Proband	Surveillance	N/A	N/A
18	7	2	10	Male	<i>TGFBR1</i>	Proband	Surveillance	N/A	N/A
19	8	1	48	Female	<i>TGFBR2</i>	Proband	Surveillance	N/A	N/A
20	8	2	9	Female	<i>TGFBR2</i>	Non-proband	Surveillance	N/A	N/A

TGFB2, Transforming growth factor β receptor-2; *CVG*, composite valve-graft replacement; *AAA*, abdominal aortic aneurysm; *DTAA*, descending thoracic aortic aneurysm; *TEVAR*, thoracic endovascular aortic repair; *TAAA*, thoracoabdominal aortic aneurysm; *SMA*, superior mesenteric artery; *AI*, aortic insufficiency; *EVAR*, endovascular aortic repair; *N/A*, not available; *CABG*, coronary artery bypass grafting.