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Original Article

Surgical Outcome and Histological Differences between Individuals with *TGFBR1* and *TGFBR2* Mutations in Loeys-Dietz Syndrome

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Purpose: To identify differences in surgical outcomes between patients with transforming growth factor-beta receptor (*TGFBR*) *1* and *TGFBR2* mutations in Loeys-Dietz syndrome (LDS).

Methods: In all, 22 LDS patients between 1998 and 2015 were divided into the two groups: *TGFBR1* (n = 11) and *TGFBR2* mutation (n = 11).

Results: The freedom from aortic reoperation was similar between the two groups (p = 0.19, log-rank). In the subanalysis, the freedom from aortic reoperation was lower in female patients with *TGFBR2* mutations (n = 6) than in other patients (p = 0.08). The freedom from aortic dissection (AD) after the initial surgery was also lower in female patients with *TGFBR2* mutation than in other patients (p = 0.025). All patients with *TGFBR2* mutations revealed grade III cystic medial necrosis (CMN), whereas 67% of patients with *TGFBR1* mutations showed CMN (p = 0.033) and only one patient had grade III (p <0.001).

Conclusion: LDS patients with *TGFBR2* mutations had higher grade of CMN than those of *TGFBR1* mutations. In particular, in female patients with *TGFBR2* mutations, AD after the initial surgery and reoperation were more frequent than those of other LDS patients.

Keywords: Loeys-Dietz syndrome, transforming growth factor-beta receptor, cystic medial necrosis, surgical outcome

Introduction

Loeys-Dietz syndrome (LDS) is one of the hereditary aortic diseases (HAD), which is caused primarily by transforming growth factor-beta receptor (*TGFBR*) *1* and *TGFBR2* mutations.[1–3] Aortic lesions are considered to have great influences on the clinical prognosis. Our previous study reported a lower free rate from aortic events after the initial aortic surgery in patients with LDS and recommended earlier surgical interventions compared

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with Marfan syndrome.[4] The current aortic management for LDS has been similar between patients with *TGFBR1* and *TGFBR2* mutations.[1,4–6] However, the international LDS registry recently revealed that female patients with lower body surface area (BSA), *TGFBR2* mutation, and severe extra-aortic features tended to have poorer prognosis.[7] However, no reports have determined clearly any differences in the surgical outcomes according to the mutation differentiation.

This study is aimed to determine differences in surgical outcomes and histological differences between LDS patients with *TGFBR1* and *TGFBR2* mutations.

Materials and Methods

The flowchart of this study population based on the exclusion criteria and method is shown in **Fig. 1**. Medical records of 304 patients aged <50 years and underwent surgeries for thoracic aortic diseases between 1998 and 2015 were investigated. Depending on the different situations, genetic screening was conducted in 163 patients (54.0%) who underwent aortic surgeries at our center and were suspected of HADs due to their younger age (<50 years) at the onset of aortic dissection (AD), family history, and physical features. Patients with inflammatory aortic disease including Takayasu arteritis and Behçet's disease, and the majority of patients with bicuspid aortic valve were excluded from the genetic screening. Among them, gene mutations were identified in 76.7% (n= 125/163) of patients: 94 (57.7%) with *FBN1* mutations; 26 (15.9%) with *TGFBR1, TGFBR2, SMAD3*, or *TGFB2* mutations; 2 (1.2%) with *COL3A1* mutations; and 9 (5.5%) with *ACTA2* mutations. A total of 32 (19.7%) patients had no detectable mutations. All of them were determined at our research laboratory center. Patients with *SMAD3* (n = 2) and *TGFB2* (n = 2) mutations were excluded from the LDS category because the mechanisms of these four gene mutations causing aneurysm or dissection are still unknown. Finally, 22 patients (13.5%) with *TGFBR1* (n = 11) and *TGFBR2* mutations (n = 11) were enrolled in this study (**Fig. 1**).

In all, 11 LDS patients with *TGFBR1* mutation were assigned to the *TGFBR1* group (8 males, 3 females; mean age at the first operation, 30 ± 9.7 years) and the other 11 patients with *TGFBR2* mutation were assigned to the *TGFBR2* group (5 males, 6 females; 25 ± 10 years). Preoperative hypertension (HT) was defined as the presence of systolic blood pressure of >140 mmHg or diastolic blood pressure of > 90 mmHg or daily use of

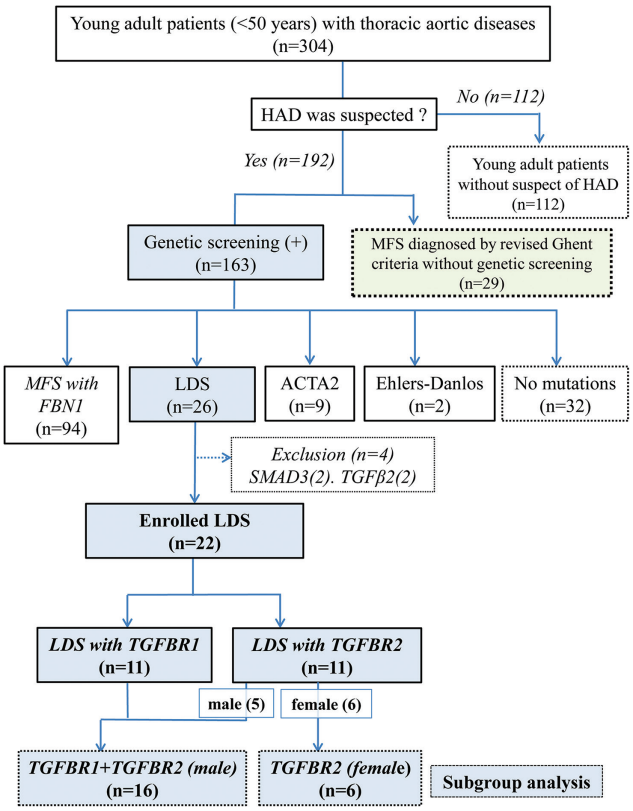

Fig. 1 Flowchart of study population and method: Based on listed exclusion criteria, 22 patients were enrolled in this study.

an antihypertensive medication. Preoperative HT was determined before diagnosing an aortic disease. Aortic root dilatation was defined as a Z-score of ≥2, a tool that correlates aortic sizes with patients' BSA scores.[1]

Patient characteristics

Preoperative characteristics and clinical features of both groups are listed in **Table 1**. At the initial surgery, the prevalence of type A AD was similar between the two groups (45.4% vs. 9.1%; p = 0.15), whereas the number of type B AD significantly smaller in the *TGFBR1* (9.1%) than in the *TGFBR2* group (54.5%) (p = 0.034). The incidence of annulo-aortic ectasia was similar between the two groups (45.4% vs. 36.4%; p = 1.00). The proportion of patients with a family history of thoracic aortic diseases tended to be more frequent in the *TGFBR1* (90.9%) than in the *TGFBR2* group (54.5%) (p = 0.081). No differences were observed in other variables (**Table 1**).

Operative techniques

Valve-sparing root replacement (VSRR) was performed through a standard median sternotomy or lower

Table 1 Preoperative characteristics and clinical features

Variable	*TGFBR1* (n = 11) No. (%)	*TGFBR2* (n = 11) No. (%)	p value
Male/female	8/3	5/6	0.39
Age (mean ± standard deviation)	30 ± 10	25 ± 10	0.32
Diagnosis at initial surgery			
AD (STA) (acute/chronic)	5 (3/2) (45.5%)	1 (1/0) (9.1%)	0.15
AD (STB) (acute/chronic)	1 (0/1) (9.1%)	6 (0/6) (54.5%)	0.034
Annulo-aortic ectasia	5 (45.5%)	4 (36.4%)	0.66
Other conditions			
Hypertension	3 (27.3%)	5 (45.5%)	0.42
Dissection during pregnancy in females	1 (33.3%)	1 (16.7%)	0.58
Root dilatation (>Z2)	7 (63.6%)	8 (72.7%)	0.68
Family history of aortic disease	10 (90.9%)	6 (54.5%)	0.081
Ectopia lentis	0	0	–
Operative procedures			
Root repair (valve sparing root repair/Bentall)	7 (5/2) (63.3%)	4 (4/0) (36.4%)	0.39
Hemiarch repair	0	1 (9.1%)	1.0
Total arch repair	3 (27.3%)	0	0.21
Descending repair	0	4 (36.4%)	0.045
Thoracoabdominal repair	1 (9.1%)	2 (18.2%)	0.61
Emergency surgery	3 (27.3%)	1 (9.1%)	0.59

AAA: abdominal aortic aneurysm; AAE: annuloaortic ectasia; AD: aortic dissection; STA: Stanford type A; STB: Stanford type B; *TGFBR*: transforming growth factor-beta receptor

mini-sternotomy with cardiopulmonary bypass (CPB) established with ascending aorta/femoral arterial cannulation in conjunction with bicaval venous drainage. In the aortic arch surgery, arterial cannulation to the right axillary artery in the axilla was usually performed with the ascending aorta and/or femoral artery cannulation for CPB. Patients were cooled to 25–28°C. Antegrade selective cerebral perfusion was employed for cerebral safety.[8] A stepwise distal aortic anastomosis was frequently used to perform a secure and easy anastomosis.[9] Patients who had thoracoabdominal aortic and descending aortic grafting were treated with 4th to 7th intercostal space thoracotomy. CPB was established with venous drainage from the femoral vein and the main pulmonary artery in conjunction with arterial return via the left axillary and femoral artery. Patients were cooled to a core temperature 18–20°C and an open proximal and/or distal aortic anastomosis was most frequently performed.

Endpoint analysis

The primary endpoint of this study was long-term aortic events, including a new AD, aortic reoperation, and aortic rupture. As the secondary endpoint, the long-term survival rate was determined, and pathohistological findings of surgical aortic specimens were also compared between the two groups. The international LDS registry showed an extremely poor prognosis in female patients and/or patients with *TGFBR2* mutations compared with other LDS patients.[7] To investigate these specific clinical courses, the patients were divided into two groups (**Fig. 1**). The follow-up rate was 100% among the survivors.

Pathohistological examination

Surgical specimens for the histopathological examination were obtained from the ascending aorta (including the Valsalva sinus and aortic arch) and/or the descending aorta to the Th10 level (excluding the infrarenal abdominal aorta). Regarding the histopathological results, including specimens sampled at the previous operations, cystic medial necrosis (CMN; defined as pooling of mucoid material), and elastin fragmentation (EF; characterized by elastin lamellae disruption) were determined. The two features were then classified into three grades (grade III, the severest), that is, according to the degree of cystic areas in patients with CMN and the amount of foci with EF in patients with EF.[10] The specimen with a small amount of media was excluded from this study because performing an accurate evaluation might be difficult. The aortic wall having a large amount of media was included in this study, although a simple

dissection flap excluded for the examination. The specimen with the severest grade from multiple samples was selected in each patient.

Data collection and statistical analysis

Data were collected from the hospital admission and outpatient medical records. All patients were followed up as outpatients either at our center or local hospitals. This retrospective observational study was approved by the institutional review board (M30-057), and individual oral and written informed consent was waived due to its retrospective design. Statistical analyses were conducted using STATA software (Stata Corp LLC, College Station, TX, USA). Categorical data were compared using the Fisher's exact test. Continuous variables were expressed as the mean ± standard deviation and compared using t-test; $p < 0.05$ was considered statistically significant. Survival rate, freedom from reoperation, and freedom from aortic operation after the initial operation were assessed using a Kaplan–Meier life-table analysis, and the log-rank test was used when comparing the subgroups.

Results

Operative findings, early morbidity, and mortality

Surgical procedures were compared between the two groups (**Table 1**). Descending thoracic aortic repair was more frequently performed in the *TGFBR2* (36.4%) than in the *TGFBR1* group (0%) ($p = 0.045$). Neither in-hospital deaths nor cerebral events occurred in both groups. VSRR was performed in five patients of the *TGFBR1* group and four patients of the *TGFBR2* group; complete atrioventricular block requiring pacemaker implantation occurred in one patient from each group. No other postoperative complications were observed (**Table 1**). Staged operation was conducted in one patient of the *TGFBR2* group, a 9-year-old boy with history of acute type A AD on chronic type B AD. He underwent VSRR and total arch replacement (TAR), followed by secondary thoracoabdominal repair within 1 year. Four emergent surgeries, including a Bentall procedure in two patients, hemiarch repair in one patient, and TAR in one patient, were performed for acute type A AD.

Late mortality

The long-term follow-up was available in 100% of survivors, and the mean follow-up time was comparable between the two groups: 95 ± 98 and 135 ± 61 months ($p = 0.63$). In the *TGFBR1* group, one patient with hyperthyroidism suddenly died, presumably from ventricular arrhythmia at 1 month postoperatively. No other deaths occurred in both groups. The freedom from all-cause mortality was similar between the two groups ($p = 0.32$, log-rank).

Aortic reoperation

During the follow-up periods, eight aortic reoperations were performed for five patients in the *TGFBR1* and 25 aortic reoperations for 10 patients in the *TGFBR2* group. The freedom from aortic reoperation was similar between the two groups ($p = 0.17$, log-rank) **(Fig. 2A)**. The details of surgical history in each group are presented in **Table 2**. In the TGFBR1 group, two redo emergency surgeries which included TAR for acute type A AD in one patient and descending thoracic aortic repair for rupture of acute type B AD in one patient were performed. In the *TGFBR2* group, six redo emergency/urgent surgeries including isolated TAR in four patients, TAR with a Bentall procedure in one patient, and TAR with VSRR in one patient were performed for acute type A AD (**Table 2**). Among these eight redo surgeries due to AD, although the AD extended to the previous anastomosis in five patients, no new entries obviously arisen from the suture line of the initial surgery were detected. In the other three patients, AD did not extend to the previous anastomotic site.

Aortic dissection

AD during the follow-up is defined as performance of any types of AD developed after the initial aortic surgeries, including recurrent AD. AD after the initial surgery was detected in three patients in the *TGFBR1* and six patients of the *TGFBR2* group during the follow-up. The freedom from AD after the initial surgery was similar between the two groups ($p = 0.55$, log-rank) **(Fig. 2B)**.

Subgroup analysis of female patients with TGFBR2

The freedom from aortic reoperation tended to be lower in female patients of the *TGFBR2* group than that in other patients ($p = 0.08$, log-rank) **(Fig. 2C)**. The freedom from AD was significantly lower in female patients of the *TGFBR2* group than that in others ($p = 0.025$, log-rank) **(Fig. 2D)**.

Details of pathohistological examination

The specimen was examined in nine patients (82%) of the *TGFBR1* group and 10 (91%) of the *TGFBR2* group. Grading of specimens in both groups is listed in **Table 2**. All patients of the *TGFBR2* group revealed grade III CMN, whereas it was found in 67% (6/9) of patients of

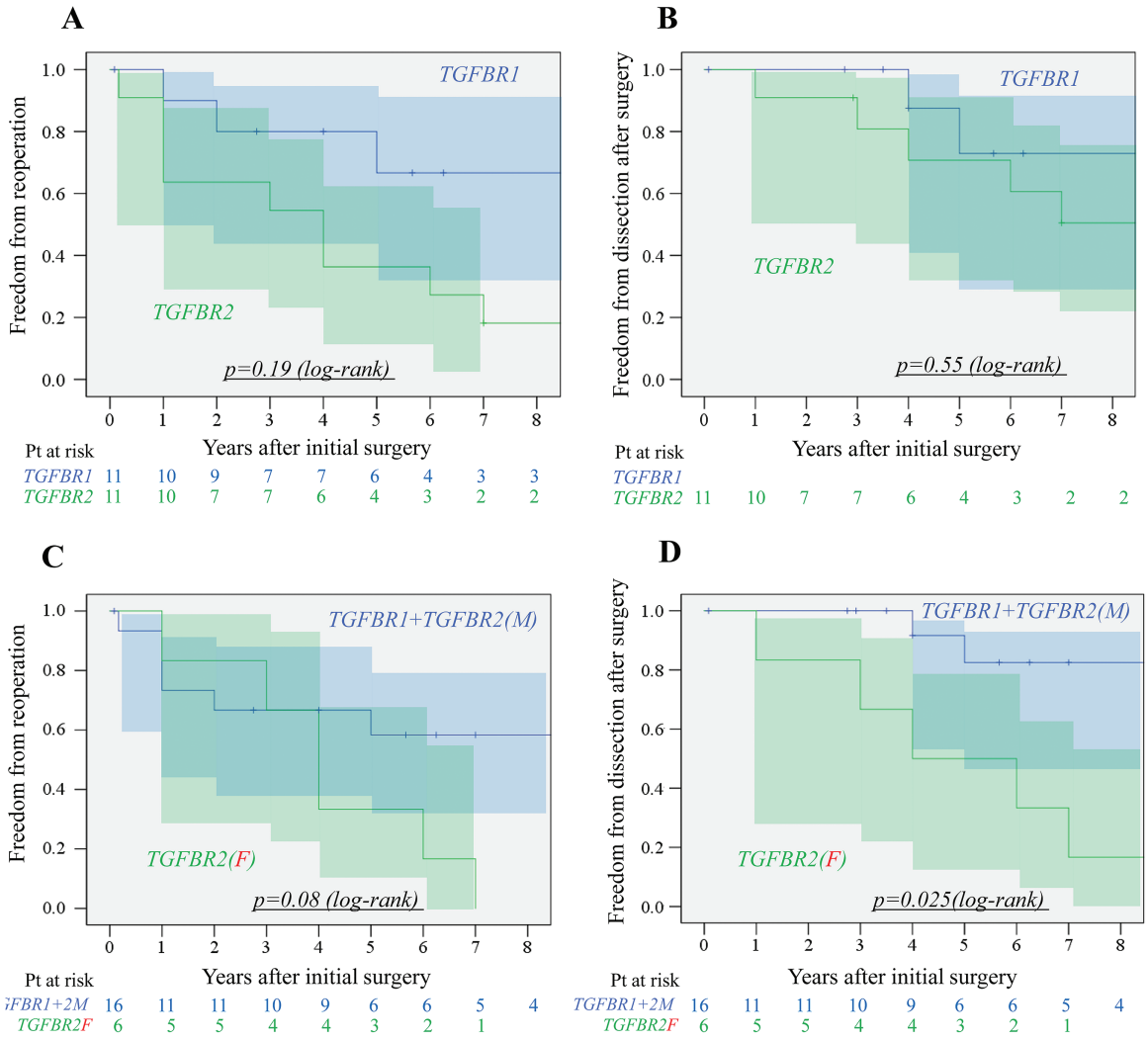

Fig. 2 Survival curves of *TGFBR 1* and *TGFBR2* cohorts: (**A**) Freedom from aortic reoperation and (**B**) freedom from AD after initial surgery. Survival curve of subanalysis *TGFBR1+TGFBR2* (male) vs. *TGFBR2* (female): (**C**) freedom from aortic reoperation and (**D**) Freedom from AD after initial surgery. AD: aortic dissection; *TGFBR*: transforming growth factor-beta receptor

the *TGFBR1* group (p = 0.033). Of these, only one patient revealed grade III (p <0.001) (**Fig. 3A**). Aortic specimens in patients with both *TGFBR1 and TGFBR2* mutations demonstrated more than Grade II EF in all patients (p = 1.0). In terms of the grade III EF, it was more frequent in the *TGFBR2* (10/10: 100%) than that in the *TGFBR1* group (5/9: 55.6%) (p = 0.033) (**Fig. 3A**). The most common specimen with grade II CMN in the *TGFBR1* group and grade III CMN in the *TGFBR2* group are presented in **Fig. 3B** and **3C**, respectively.

Discussion

LDS is a HAD caused by *TGFBR1* or *TGFBR2* mutation and no differences in phenotypes are observed between individuals with *TGFBR1* and *TGFBR2* mutations.[1] However, Tran-Fadulu et al.[11] reported on some clinical differences between them, demonstrating that male patients died at younger age than females in families with *TGFBR1* mutations, and that more patients with *TGFBR2* mutations develop AD even at the aortic diameters <5.0 cm than ones with *TGFBR1* mutations. However, no causes of death were described, and the causes of such clinical differences remain unclear. Recently, the international registry of 441 LDS patients revealed some differences between patients with these mutations.[7] Jondeau et al. demonstrated that patients with *TGFBR1* or *TGFBR2* mutation had the same prevalence of systemic features and survival, and recommended earlier preventive aortic surgery at the size of 40 mm in female patients with *TGFBR2* mutation and lower BSA.

Table 2 Details of surgical history and grading of the specimens in both *TGFBR1* and *TGFBR2 groups*

Variable	Age	Gen	Initial surgery	Second	Third	Fourth	Fifth	CMN Ascending	EF Ascending	CMN Descending	EF Descending
TGFBR1											
1	32	M	VSRR					III	III	N/A	N/A
2	46	M	TAR*					II	II	N/A	N/A
3	26	M	VSRR					II	II	N/A	N/A
4	25	M	VSRR					I	II	N/A	N/A
5	27	M	VSRR					No CMN	III	N/A	N/A
6	32	M	Bentall + TAR*	TAAAR				No CMN	III	N/A	N/A
7	38	F	TAR	TAAAR**				N/A	N/A	II	II
8	36	F	TAAAR					N/A	N/A	II	III
9	40	F	TAR	DTAAR				N/A	N/A	No CMN	III
10	15	M	VSRR	TAR**	TAAAR	Re TAAAR		N/A	N/A	N/A	N/A
11	16	M	Bentall*	TAR	Re-Bentall			N/A	N/A	N/A	N/A
TGFBR2											
1	19	M	VSRR	Bentall				III	III	N/A	N/A
2	36	M	TAAAR	Bentall +TAR**	TAAAR			III	III	N/A	N/A
3	22	M	VSRR					III	III	N/A	N/A
4	39	F	DTAAR	TAR**	TAAAR	VSRR		III	III	N/A	N/A
5	19	F	VSRR	TAR**				III	III	N/A	N/A
6	39	M	DTAAR	Re DTAAR	TEVAR	TAAAR		III	III	III	III
7	15	F	VSRR	TAR**	DTAAR	TAAAR		III	III	II	III
8	20	F	HAR*	VSRR	TAR	TAAAR		III	III	No CMN	III
9	9	M	TAAAR	VSRR+TAR				III	III	No CMN	III
10	30	F	DTAAR	VSRR +TAR**	Re DTAAR	Bentall	TAAAR	N/A	N/A	III	III
11	30	F	DTAAR	TAR**	TAAAR	Bentall	TEVAR	N/A	N/A	N/A	N/A

*Emergent surgery at initial surgery, **Emergent surgery due to type A/B dissection at redo surgery. AVR: aortic valve replacement; CMN: cystic medial necrosis; DTAAR: descending aortic repair; EF: elastin fragmentation; F: female; Gen: gender; M: male; N/A: no available specimen; TAR: total arch repair; TAAAR: thoracoabdominal aortic repair; *TGFBR:* transforming growth factor-beta receptor; VSRR: valve-sparing root replacement

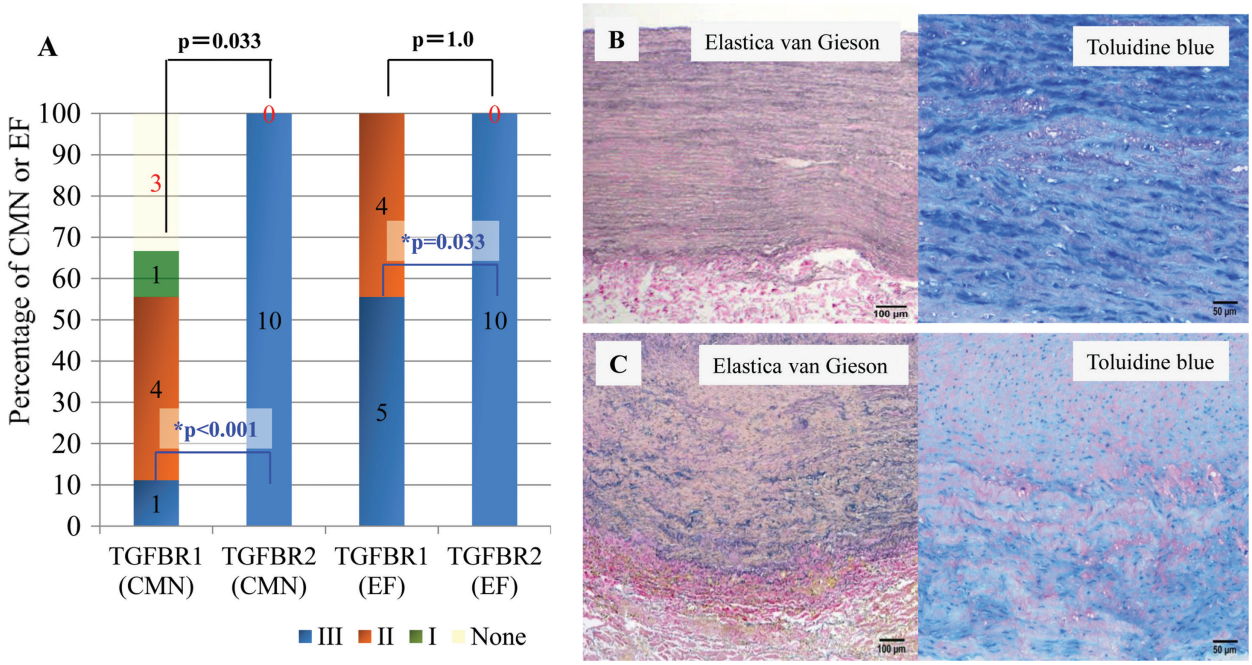

Fig. 3 (**A**) Histological grades of CMN and EF: comparison between *TGFBR1* and *TGFBR2* cohort; the aorta of *TGFBR1* mutations revealed CMN in minor than that of *TGFBR2* mutations (p = 0.033), and only one specimen (11%: 1/9) of them revealed grade III CMN. In terms of EF, specimens of both *TGFBR1* and *TGFBR2* demonstrated more than grade II EF in all cases (p = 1.0). When limited to grade III EF, it was significantly fewer in *TGFBR1* (5/9: 55.6%) than *TGFBR2* mutations (p=0.033). (**B, C**) A representative photomicrograph of LDS aortopathy carrying *TGFBR1* and *TGFBR2* mutations: Upper panel; (**B**) the ascending aorta in LDS carrying *TGFBR1* mutation stained with Elastica van Gieson and toluidine blue show grade II CMN and grade II EF, Lower panel; (**C**) the ascending aorta in LDS carrying *TGFBR2* mutation stained with Elastica van Gieson and toluidine blue show grade III CMN and grade III EF. CMN: cystic medial necrosis; EF: elastin fragmentation; LDS: Loeys-Dietz syndrome; *TGFBR*: transforming growth factor-beta receptor

In this study, similar to the previous study,[7] no significant differences in the survival rates were observed between the two mutations. Moreover, there were also no differences in the freedom from reoperation and AD after the initial surgery. However, female patients with *TGFBR2* mutation, who were more notable compared with the other LDS patients, tended to have a lower free rate from aortic reoperation and AD after the initial surgery. These results suggest that aortic structures might differ in patients with both mutations. In other words, patients with *TGFBR2* mutation, especially females, might potentially have severer aortic pathologies.

In terms of aortic pathology, type B AD was more frequent in patients with *TGFBR2* mutation compared to those with *TGFBR1* mutation in this study, which suggested that aortic structures might differ between the two mutations. Previously, similar consequences were demonstrated in a large cohort.[7] Regarding the type A AD, as the first aortic event, the international registry of acute AD showed a smaller aortic diameter before the AD onset in patients with *TGFBR2* mutation than those with *TGFBR1* mutation (51.8 ± 13.4 mm vs. 68.3 ± 23.0 mm; p = 0.06),[7] due to some structural differences in the aorta with both mutations.

In this study, the most prominent observation was on pathohistological differences in the degree of CMN between the two mutations. Initial recognition of tissue disorders underlying the aortic dilation in LDS is medial degeneration, which is characterized by findings of EF, loss of smooth muscle cell, and glycosaminoglycan replacement. The presence of medial degeneration from the extracellular pooling of glycosaminoglycan-rich basophilic solid and insufficient cells leads to CMN.[12] In general, CMN is occasionally found in non-HAD patients. Becker et al.[10] reported that CMN was found in approximately 60% of the normal aorta for all generations. More commonly, CMN is also observed in patients with HADs, which is related to a higher risk for aortic events.[13–15] In addition, EF is characterized by damaged elastin lamella and is one of the categories indicating medium changes of the aorta and reflects intimal degeneration and CMN.[10] Recently, Wanga et al.[16] hypothesized that EF plays a

causal role in the aortic calcification in MFS and proposed microcalcification as a novel imaging marker to monitor local EF and thus predict aortic events in patients with MFS. Regarding the relationship between EF and LDS, Nakajima et al.[17] reported the pathohistological findings of the aortic wall, showing EF in LDS with *TGFBR1* mutation. In this study population, fewer specimens of the aorta with *TGFBR1* mutations revealed CMN compared with aortic specimens with *TGFBR2* mutations. In addition, grade III CMN was observed in only 11% of patients with *TGFBR1* mutations and 100% of patients with *TGFBR2* mutations. This difference might be related to the dissimilarities of surgical outcomes between *TGFBR1* and *TGFBR2* mutations. Conversely, specimens with both *TGFBR1* and *TGFBR2* mutations demonstrated more than the average EF in all patients. This finding indicates that both tissue abnormalities are advanced similarly.[10,16,17] However, when limited to grade III EF, grade III EF was more frequent in *TGFBR2* mutations than in *TGFBR1* mutations. Therefore, this difference might be related to differences in surgical outcomes between two mutations.

Study Limitations

This was a retrospective study on a specific patient cohort, and the sample size was limited. Proper assessment to obtain reproducible results of histopathological findings in these types of patients will require a larger cohort.

Conclusion

Patients with LDS with *TGFBR2* mutation had a higher grade of CMN than those with *TGFBR1* mutation. When limited to female patients with *TGFBR2* mutations, AD after the initial surgery occurred more frequently compared to other LDS patients.

Disclosure Statement

All authors have no conflict of interest.

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