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Surgical Treatment of Patients Enrolled in the National Registry of Genetically Triggered Thoracic Aortic Conditions (GenTAC)

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Abstract

Background—Genetic disorders are an important cause of thoracic aortic aneurysms (TAAs) in young patients. Despite advances in the treatment of genetically triggered TAAs, the optimal syndrome-specific treatment approach remains undefined. We used data from the NIH-funded, multicenter National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) to characterize the contemporary surgical treatment of patients with genetically triggered TAAs.

Methods—GenTAC's aim is to collect longitudinal clinical data and banked biospecimens from 2800 patients with genetically triggered TAAs. We analyzed data from all patients enrolled in GenTAC to date whose clinical data were available (n=606; mean age, 37.5 years).

Results—The patients' primary diagnoses included Marfan syndrome (35.8%), bicuspid aortic valve with aneurysm (29.2%), and familial TAAs and dissections (10.7%). More than half of patients (56.4%) had undergone at least 1 operation; the most common indications were aneurysm (85.7%), valve dysfunction (65.8%), and dissection (25.4%). Surgical procedures included replacement of the aortic root (50.6%), ascending aorta (64.8%), aortic arch (27.9%), and

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descending or thoracoabdominal aorta (12.4%). Syndrome-specific differences in age, indications for surgery, and procedure type were identified.

Conclusions—Patients with genetically transmitted TAAs evaluated in tertiary care centers frequently undergo surgery. Aneurysm repairs most commonly involve the aortic root and ascending aorta; distal repairs are less common. Like TAAs themselves, complications of TAAs, including dissection and aortic valve dysfunction, are important indications for surgery. Future studies will focus on syndrome- and gene-specific phenotypes, biomarkers, treatments, and outcomes to improve the treatment of patients with TAAs.

Keywords

Aneurysm; aortic operation; genetics

Introduction

Thoracic aortic aneurysms (TAAs) predispose patients to life-threatening aortic complications, including aortic dissection and rupture [1,2]. A TAA that involves the aortic root can also cause aortic regurgitation and secondary heart failure [3]. Gene mutations can trigger TAAs as part of a syndrome, such as Marfan syndrome, or in the absence of syndromic features, in which cases the lesions are termed familial thoracic aortic aneurysms and dissections (FTAAD) [4–6]. Although hypertension and atherosclerosis are important risk factors for TAAs beyond the aortic root in the elderly, genetic disorders are the cause of TAAs in many young and middle-aged patients [5,7,8].

Although diagnostic and treatment advances have dramatically improved care for patients with genetically triggered TAAs, many questions remain about how best to identify and treat these disorders. To help address these questions, we have developed the multicenter, longitudinal National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) [9]. Total enrollment through 5 regional clinical centers in the United States is expected to exceed 2800 patients by the year 2010. The registry has established a biospecimen repository and bioinformatics infrastructure to enable research to determine best practices for optimal clinical management of genetically triggered TAAs and related complications. In this study, we used GenTAC data to characterize the contemporary surgical treatment of patients with genetically triggered thoracic aortic disease.

Material and Methods

Institutional Review Board approval was obtained for this study at each of the 5 participating GenTAC regional clinical centers. Individual informed consent was obtained from each GenTAC Registry patient.

GenTAC Registry

The GenTAC Registry contains longitudinal observational data on patients with conditions related to genetically induced TAAs [9]. The National Heart Lung and Blood Institute and the National Institute of Arthritis and Musculoskeletal and Skin Diseases are co-sponsors of GenTAC. Patients are recruited from 5 regional clinical centers that treat patients from a wide geographic catchment area within the United States: Johns Hopkins University, Oregon Health & Science University, University of Pennsylvania, University of Texas Health Science Center at Houston/Baylor College of Medicine, and Weill Cornell Medical College. Research Triangle Institute International serves as the data coordinating center

responsible for data management, coordination of training, logistics, and statistical design and analysis.

The targeted enrollment of patients includes adults and children who fall into 1 or more of 12 diagnosis categories, including Marfan syndrome, Loeys-Dietz syndrome, Ehlers-Danlos syndrome, Turner syndrome, bicuspid aortic valve (BAV), and FTAAD [10–25]. Available clinical data, imaging results, and blood and tissue samples from each patient are processed and stored by GenTAC to provide a resource that combines clinical and biological data from a large and diverse population of patients with inherited TAA disorders.

Patients

As of January 2009, 994 patients have been enrolled in GenTAC; 606 of these patients have clinical data available for analysis. We analyzed these, focusing on surgical procedure data.

Analysis

We used SAS software (SAS Institute, Inc.; Cary, NC) to extract data from the secure ESN database, to create reports and summary tables, and to perform other ad hoc statistical analyses. To examine between-groups differences in outcomes, we used proportions tests, 2-sample *t* tests, and Tukey multiple comparison tests. The experiment-wise error rate was controlled at the 0.05 level. For data security purposes, all analyses were performed and all data were stored in a password-protected remote workspace.

Results

Diagnostic Groups

The 606 patients represented 12 different primary diagnosis categories (Table 1). Three of the diagnostic groups describe patients with BAV: in association with aortic coarctation, with family history, and without known family history. For the purposes of BAV diagnosis classification, GenTAC defines family as any first degree relative with thoracic aortic enlargement 2 SD above normal based on nomograms, prior TAA repair or dissection, significant enlargement compared to adjacent area, BAV, or aortic coarctation.

The 4 most common primary diagnoses were Marfan syndrome, BAV without known family history, other TAAs and dissections in patients < 50 years of age, and FTAAD. Patients in these 4 primary diagnosis groups constituted more than 80% of all patients enrolled in the GenTAC Registry at the time of this analysis. The other primary diagnoses were uncommon, especially Shprintzen-Goldberg syndrome, other congenital heart disease with TAA, and BAV with coarctation, each of which was the primary diagnosis in no more than 1% of the patients.

Prevalence of Previous Cardiovascular Surgery

More than half of all patients had previously undergone a cardiovascular surgical procedure at the time of their enrollment into GenTAC. This was also true in all 4 of the largest primary diagnosis groups (Table 1). The majority of patients in these groups had undergone their first cardiovascular operation before age 50 (Fig 1).

Mean age at the time of first operation varied between the diagnosis groups (Table 2) and was lowest in the Loeys-Dietz syndrome, other congenital heart disease, BAV with coarctation, and Turner syndrome groups. Patients in the Loeys-Dietz syndrome, BAV with coarctation, and Turner syndrome groups had a significantly lower mean age at first operation than patients in the BAV without known family history and FTAAD diagnosis

groups. Patients with FTAAD or BAV without known family history had higher mean age at operation than Marfan syndrome patients.

Indications

Detailed information on individual surgical procedures was available from 98 Marfan syndrome patients, 72 patients with BAV without known family history, 32 patients with other TAAs, 30 patients with FTAAD, and fewer patients in other diagnostic categories. The remainder of the analysis focused on patients in the 4 most commonly represented diagnostic groups because low enrollment limited meaningful analysis of patients in other diagnostic categories.

Aortic aneurysm was the most common indication for surgery in patients with Marfan syndrome, other TAAs, and FTAAD (Fig 2). Patients with Marfan syndrome were more likely to have aneurysm as an indication for surgery than other patients ($p < 0.0001$ for all comparisons). Valve dysfunction, mostly aortic regurgitation associated with aortic root aneurysm, was also a frequent indication for surgery in both Marfan and FTAAD patients.

For patients with BAV without known family history, aortic valve dysfunction was the most common indication for surgery. In this group, 59.4% had aortic stenosis, and 56.3% had aortic valve regurgitation. The BAV patients were significantly more likely to have valve dysfunction as a surgical indication than the Marfan, other TAA, and FTAAD patients ($p < 0.0001$ for all comparisons). Most of the BAV patients (79.2%) also had an aortic aneurysm as an indication for surgery.

Dissection was the third most common indication for surgery in the 4 diagnostic groups. Patients with BAV were significantly less likely to present with dissection than patients with FTAAD, Marfan syndrome, and other TAA. Failure of prior aortic repair was an uncommon indication for surgery, occurring in 10.2% of Marfan patients, 2.8% of BAV patients, and 3.1% of other TAA patients.

Procedures

The frequency of aortic root replacement differed among the 4 largest primary diagnosis groups (Fig 3, Table 3). Roughly 80% of Marfan syndrome patients who underwent surgery had aortic root replacement of some form. Conventional valve-replacing aortic root replacement was performed in 48.0% of these patients. Valve-sparing aortic root replacement, most commonly by using a reimplantation technique, was performed in 30.6%. Ascending aorta replacement was performed in 45.9% of cases, while procedures involving the more distal arch, descending thoracic aorta, and thoracoabdominal aorta were performed less frequently. Relatively few patients underwent mitral valve repair (9.2%) or replacement (10.2%), and even fewer underwent isolated aortic valve repair (5.1%) or replacement (8.2%). Marfan patients were significantly more likely to have undergone valve-sparing aortic root, descending thoracic aorta, and thoracoabdominal aorta replacement than BAV patients.

Aortic root replacement was less common in patients with BAV without known family history. Conventional aortic root replacement was performed in 43.1%, whereas valve-sparing aortic root replacement was performed in 8.3%. Ascending aorta replacement was the most commonly performed aortic procedure in this group, having been performed in 69.4%. Aortic arch replacement was performed in 50.0%. No descending thoracic aortic or thoracoabdominal aortic procedures were performed in these patients. Ascending aorta and aortic arch replacement were performed more commonly in BAV patients than in Marfan patients (Table 3).

Patients in the FTAAD group underwent aortic root replacement in 36.7% of cases. Valve-sparing aortic root replacement was performed in 23.3% of these patients, and ascending aorta replacement was performed in 53.3%. Aortic arch, descending thoracic aorta, and thoracoabdominal aorta replacement were performed in 26.7%, 10.0%, and 20.0%, respectively. Aortic valve repair and replacement were performed in 13.3% and 6.7%, respectively. No mitral valve procedures were performed in this group.

Patients in the other TAAs group had the lowest frequency of aortic root replacement (25.0%). Ascending aorta replacement was the most common previous procedure in these patients (50.0%). Aortic arch, descending thoracic aorta, and thoracoabdominal aorta replacement were performed in 21.9%, 3.1%, and 9.4% of cases, respectively. Aortic valve repair and replacement were performed in 12.5% and 15.6%, respectively. No mitral valve procedures were performed in this group.

Mean aortic diameter differed among patients who underwent various aortic replacement procedures (Fig 4). The mean aortic root diameter for all patients who underwent conventional aortic root replacement was 5.96 cm, which was significantly larger than the aortic root diameter of patients who underwent valve-sparing aortic root replacement (5.14 cm). The mean aortic diameter of patients who underwent descending thoracic aorta replacement was in the 5-cm range. Although abnormally large, these aortic sizes are smaller than those listed in the published criteria for aneurysm repair, even for patients with genetically-triggered aneurysms [26].

Outcomes

Analysis of postoperative outcomes is limited because these data were not collected prospectively. In addition, many patients were enrolled after their operations, so the group is heavily biased toward survivors of surgery. In fact, no patient with Marfan syndrome, BAV without known family history, or familial TAA or dissection has enrolled in GenTAC and subsequently not survived surgery (Table 4). Among these survivors, however, reported complications were uncommon, with the exception of a relatively high rate of re-exploration for bleeding in Marfan patients (99%) and BAV patients (6.8%).

Comment

The treatment of genetically triggered thoracic aortic lesions is complex and is associated with high rates of morbidity, mortality, and surgical intervention. More than half of patients in each of our diagnostic groups had undergone at least 1 cardiovascular procedure. Although there was some variability in the age at which their first operation was performed, the majority of these patients were operated on as young adults.

For patients with Marfan syndrome, other TAAs, and FTAAD, a proximal aneurysm with or without associated aortic regurgitation was the most common indication for surgery. Patients with BAV without known family history had a higher frequency of isolated aortic valve dysfunction. The proximal aorta was the most common location for aneurysm repair; arch aneurysm, descending TAA, and thoracoabdominal aortic aneurysm repairs were less common. Valve-sparing aortic root replacement techniques have been rapidly adopted and were used in many GenTAC registry patients [27]. Conversely, no patient with Marfan syndrome, BAV without known family history, other TAA, or FTAAD enrolled in GenTAC has been reported to have had an endovascular aneurysm repair to date. The incidence of repair failures and reported complications is gratifyingly low, with the exception of the need for re-exploration for bleeding.

There were significant differences among diagnosis groups with regard to age at the time of first operation, indication for surgery, and specific aortic procedure performed. Identifying these unique characteristics of the various diagnosis groups enrolled in the registry is an important goal of GenTAC. By using GenTAC to define the phenotype and natural history of these disorders, disease-specific clinical management can be refined further.

This study has limitations related to the GenTAC registry design. Historical clinical data, including operative details, abstracted from medical records may be less accurate than prospectively collected data. In addition, patients were enrolled through 1 of 5 regional clinical centers participating in GenTAC; the treatments and outcomes described in this report may have been biased by the clinical practices and guidelines used at the enrolling centers. Additionally, at several GenTAC sites, patients are enrolled through surgery practices, likely leading to a bias toward enrolling surgical patients rather than medically treated patients. Also, there was no control group of patients with non-genetically triggered TAAs. Longitudinal follow-up is planned in the coming years, which may ameliorate several of these limitations in future GenTAC studies.

The overarching goal of the GenTAC Registry is to serve as a resource to advance the treatment of patients with genetically triggered thoracic aneurysms. Research projects using the Registry's resources are currently being initiated by the GenTAC steering committee. These projects include phenotype studies, studies evaluating plasma biomarkers and their association with TAA events in Marfan patients, and the use of single nucleotide polymorphisms to search for as-yet unidentified genetic causes of TAAs. Additional proposals are being solicited from the greater cardiovascular community [9]. As clinical information, such as that contained in this report, is integrated with genetic and biomarker data, our understanding of gene-specific clinical manifestations will lead to improved syndrome-specific treatment approaches.

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Fig 1.

Age at first operation in selected diagnosis groups in the GenTAC Registry. The + signs denote mean age in years; the lines within the gray boxes denote median age in years. The gray boxes span the 25th to 75th percentiles. There were several significant differences between diagnosis groups in mean age at the time of first operation (Table 2). (BAVHis = bicuspid aortic valve with known family history; BAVNoHis = bicuspid aortic valve without known family history; EDS = Ehlers-Danlos syndrome; FBN1 = fibrillin-1, transforming growth factor beta receptor 1 or 2, actin alpha 2, or myosin heavy chain 11 mutation; FTAA_D = familial thoracic aortic aneurysms and dissections; LDS = Loeys-Dietz syndrome; Marfan = Marfan syndrome; OthAneu = other aneurysms and dissections in patients <50 years of age; OthCHD = other congenital heart disease; Turner = Turner syndrome.)

Fig 2.

Indications for surgery among patients with Marfan syndrome, BAV without known family history, other TAAs, and FTAAD in GenTAC. Patients with Marfan syndrome were significantly more likely to have aneurysm as an indication for surgery than other patients ($p < 0.0001$) (#). Patients with BAV were significantly less likely than patients with FTAAD ($p = 0.0065$), Marfan syndrome ($p = 0.0416$), and other TAA ($p = 0.0117$).(*) and more likely to present with valve dysfunction ($p < 0.0001$ for all comparisons) (^).

Fig 3.

Surgical procedures performed for patients with Marfan syndrome, BAV without known family history, other TAAs, and FTAAD in the GenTAC patients. Several significant differences in procedure prevalence were found between various diagnosis groups (*) (see Table 3 for summary). (AVR = aortic valve replacement; MVR = mitral valve replacement; Valve sparing aortic root = valve-sparing aortic root replacement; Asc = ascending; DTA = descending thoracic aorta; TAAA = thoracoabdominal aorta; TAA = thoracic aortic aneurysm.)

Fig 4. Mean aortic diameters of patients with Marfan syndrome, BAV without known family history, other TAAs, and FTAAD at the time of operation. Patients who underwent aortic root replacement had significantly larger aortic diameter than patients who underwent valve-sparing aortic root replacement ($p = 0.0029$) (*). (Valve sparing aortic root = valve-sparing aortic root replacement; DTA = descending thoracic aorta; TAAA = thoracoabdominal aortic aneurysm)

Table 1

Disorders, Demographic Characteristics, and Previous Cardiovascular Surgical Procedures Among Patients Enrolled in the GenTAC Registry

Primary Diagnosis	n (%)	Mean Age at Enrollment	Percent Male	Percent Caucasian	Previous Surgery, n (%)
Marfan syndrome	217 (35.8)	34.5	51.6	91.7	117 (53.9)
BAV without known family history	153 (25.2)	42.8	79.7	94.1	100 (65.4)
Other TAAs and dissections in patients < 50 years of age	74 (12.2)	33.6	71.6	85.1	43 (58.1)
FTAAD	65 (10.7)	48.3	72.3	95.4	35 (53.8)
Ehlers-Danlos syndrome	35 (5.6)	32.5	23.5	94.1	7 (20.6)
BAV with known family history	18 (3.0)	44.3	61.1	100.0	13 (72.2)
Tumer syndrome	15 (2.5)	28.7	6.7	100.0	7 (46.7)
Loeys-Dietz syndrome	10 (1.7)	13.6	30.0	100.0	6 (66.7)
FBNI, TGFBRI, TGFB2, ACTA2, or MYH11 mutation ^a	7 (1.2)	33.5	42.9	85.7	2 (28.6)
BAV with coarctation	6 (1.0)	23.3	66.7	83.3	6 (100)
Other congenital heart disease	5 (0.8)	36.8	80.0	80.0	4 (80.0)
Shprintzen-Goldberg syndrome	1 (0.2)	16.6	100.0	100.0	1 (100.0)
Total	606 (100)	37.5	61.0	92.4	341 (56.5)

^aThese patients had mutations but did not meet diagnostic criteria for any of the syndromic groups.

ACTA2 = alpha-actin 2; BAV = bicuspid aortic valve; FBNI = fibrillin-1; FTAAD = familial thoracic aortic aneurysms and dissections; MYH11 = myosin heavy chain 11; TAA = thoracic aortic aneurysm; TGFBRI = transforming growth factor-beta receptor 1; TGFB2 = transforming growth factor-beta receptor 2.

Table 2Significant Differences in Mean Age at First Operation Between Diagnosis Groups^a

Diagnosis Group 1	Diagnosis Group 2	Mean difference (95% CI)
Turner syndrome	FTAAD	-28.68 (-48.90, -8.47)
Turner syndrome	BAV without known family history	-21.52 (-40.61, -2.42)
BAV with coarctation	FTAAD	-36.36 (-62.00, -10.73)
BAV with coarctation	BAV without known family history	-29.19 (-53.95, -4.44)
BAV with coarctation	BAV with known family history	-28.17 (-56.29, -0.05)
Loeys-Dietz syndrome	Ehlers-Danlos syndrome	-40.15 (-79.47, -0.83)
Loeys-Dietz syndrome	FTAAD	-39.48 (-61.02, -17.94)
Loeys-Dietz syndrome	BAV without known family history	-32.31 (-52.80, -11.83)
Loeys-Dietz syndrome	BAV with known family history	-31.29 (-55.73, -6.85)
Loeys-Dietz syndrome	Other TAAs and dissections in patients <50 years old	-22.25 (-43.67, -0.82)
Loeys-Dietz syndrome	Marfan syndrome	-22.13 (-43.39, 1.88)
Other congenital heart disease	FTAAD	-40.39 (-75.56, -5.22)
Shprintzen-Goldberg syndrome	FTAAD	-51.20 (-100.15, -2.24)
FTAAD	Other TAAs and dissections in patients <50 years old	17.24 (5.00, 29.47)
FTAAD	Marfan syndrome	17.34 (7.30, 27.40)
BAV without known family history	Marfan syndrome	10.18 (2.64, 17.71)

^aNo other comparisons revealed significant differences.

BAV = bicuspid aortic valve; CI = confidence interval; FTAAD = familial thoracic aortic aneurysms and dissections; TAA = thoracic aortic aneurysm.

Table 3

Significant Differences in the Frequency of Aorta Replacement Procedures Among the Four Largest Diagnosis Groups^a

Procedure	Diagnosis Group 1 ^b	Diagnosis Group 2	<i>p</i> -value
Aortic root replacement	Marfan syndrome	Other TAAs	0.0225
Valve-sparing aortic root replacement	Marfan syndrome	BAV without known family history	<0.0001
	FTAAD	BAV without known family history	<0.0001
Ascending aorta replacement	BAV without known family history	Marfan syndrome	0.0023
Aortic arch replacement	BAV without known family history	Marfan syndrome	<0.0001
	BAV without known family history	Other TAAs	0.007
	BAV without known family history	FTAAD	0.003
Descending thoracic aorta replacement	Marfan syndrome	BAV without known family history	0.0328
	FTAAD	BAV without known family history	0.0412
Thoracoabdominal aorta replacement	Marfan syndrome	BAV without known family history	0.0013
	Other TAAs	BAV without known family history	0.0084
	FTAAD	BAV without known family history	<0.0001

^aNo other differences were statistically significant.

^bFor all comparisons, the specified procedure was more common in Diagnosis Group 1 than in Diagnosis Group 2.

BAV = bicuspid aortic valve; FTAAD = familial thoracic aortic aneurysms and dissections; TAA = thoracic aortic aneurysm.

Table 4

Reported Postoperative Outcomes in Patients With Marfan Syndrome, BAV Without Known Family History, and FTAAD in GenTAC

Primary Diagnosis	Mortality (%)	Mean Length of Stay (Days)	Myocardial Infarction (%)	Stroke (%)	Prolonged Intubation (%)	Acute Renal Failure (%)	Reexploration for Bleeding (%)
Marfan syndrome	0	8.91	0	2.0	5.9	3.0	9.9
BAV without known family history	0	6.85	0	2.3	4.5	2.3	6.8
FTAAD	0	7.47	0	4.3	0	4.3	0

BAV = bicuspid aortic valve; FTAAD = familial thoracic aortic aneurysms and dissections.