Familial Nonsyndromic Thoracic Aortic Aneurysms
Unraveling the Mystery and Defining Long-Term Outcome*

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A multifactorial disease, thoracic aortic aneurysms (TAA) involve complex interactions between genetic and hemodynamic factors. TAA is associated with a wide range of underlying conditions including hypertension, bicuspid aortic valve aneurysm (BAV), and several genetic disorders. Despite progressive dilation, aortic aneurysms usually remain asymptomatic until dissection or rupture occurs. Timely recognition of TAA can be lifesaving due to the high mortality rate secondary to aortic complications. Effective prophylactic surgical interventions are available, but their implementation is hampered by difficulties in identifying patients. Although dysmorphic characteristics on physical examination can aid the identification of a possible genetic etiology, familial nonsyndromic TAA (NS-TAA) are more difficult to diagnose.

In 1997, Biddinger et al. (1) reported proband first-degree relatives were at higher risk of thoracic aortic aneurysms and sudden death compared with control groups. Other studies described a 20% to 25% prevalence of positive family history of aortic disease in patients with NS-TAA (2-4). The mode of inheritance is autosomal dominant with variable clinical presentation and incomplete penetrance (5). Patients with familial NS-TAA were younger at their initial aneurysm than those with sporadic TAA and more frequently had proximal aortic involvement. However, these studies were retrospective, based on interviewing relatives by telephone (2) and, in most of the families studied, prevalence of hypertension was high. One point that warrants discussion: the possibility of noninclusion of asymptomatic aneurysms in their pedigree analysis because it is possible that some family members may have undetected TAA.

In this issue of the Journal, Sherrah et al. (6) compare a large series of NS-TAA (n = 311), Marfan syndrome (n = 221), and BAV patients with aorta dilation (n = 228) in a prospective study carried out at a single center over 26 years. In that series, Marfan syndrome patients were diagnosed at a younger age and with a smaller aortic diameter; however, aortic dissection was more common at presentation in the NS-TAA group. This finding may be justified given that 44% of Marfan patients were diagnosed from family screening versus 29% in NS-TAA. These results highlight the difficulty in diagnosing NS-TAA as opposed to BAV or Marfan syndrome and emphasize the crucial role of a systematic family history evaluation.

Genetic analyses over the last decade have contributed greatly to the understanding of some TAA diseases, mainly in syndromic disorders. Unfortunately, the genetic basis of nonsyndromic TAA is more complex and genetic analysis identifies a mutation in only 15% to 20% of patients (5,7). In the series reported on by Sherrah et al. (6), only 18 of 89 (20%) patients had a mutation identified on genetic testing. Currently, 9 genes have been identified as causing NS-TAA (5,7,8). Four of these genes have roles in the contractile apparatus of vascular smooth cells in the aortic wall. The first gene to be identified was myosin heavy chain 11 (MYH11). Less than 1% of all NS-TAAs are explained by defects in MYH11, and the diameter of the aorta prior to dissection is usually >5 cm. Mutation in smooth muscle alpha-actin

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Another rare cause of TAA is MLCK gene mutation. This gene encodes the vascular smooth muscle cell-specific myosin light-chain kinase and accounts for <1% of all TAA. New genes have been implicated in the pathogenesis of TAA, too, and it is anticipated that more genes in several pathways will be identified. Although most of them configure the NS-TAA, it remains essential to identify the mutation as not all mutated genes carry the same vascular risk. It is increasingly important to establish the indications and limitations of genetic testing in daily practice. The absence of gene-specific clinical manifestations and the large number of plausible genes hamper targeted gene testing in NS-TAA, resulting in a costly, time-consuming process. In these patients, panel testing may facilitate an easier and more rapid study of the molecular cause underlying hereditary TAA.

Several studies have shown that patients with a family history of aortic aneurysms have faster aneurysm growth rates compared with patients with sporadic TAA (2,4) and similar to patients with Marfan syndrome. However, the natural history and clinical events of NS-TAA has not been well established. In the study by Sherrah et al. (6), a total of 687 patients with TAA were prospectively enrolled and followed for a mean of 7 years. Their main finding was that mortality was comparable for Marfan syndrome and NS-TAA, but both were higher than for BAV patients. Although comparison was made to BAV patients with aortic dilation, it may have been more interesting to compare complications of familial NS-TAA with sporadic TAA. Additionally, a familial history of aortic dissection implied a 50% higher mortality risk than no family history. At 10 years, the aortic dissection rate during clinical surveillance was 7.9% and 3.6% for Marfan and NS-TAA, respectively. No differences were observed between entities for elective surgery; however, Marfan patients were more than a decade younger at the time of elective surgery.

The results of this study reinforce the importance of clinicians obtaining a detailed family history and recommend systematic screening of first-degree relatives, even in the absence of features of syndromic genetic disorders, particularly if TAA diagnosis is made in young adults without evident risk factors. However, new evidence is required to analyze the benefits of different imaging screening protocols to be performed in first-degree relatives of patients with TAA, including the entire aorta, cerebrovascular arteries, and arterial branches originating from the aorta, depending on vascular involvement of the proband and the gene mutated in the family.

An interesting contribution of this new study is the mortality risk score based on the type of aortopathy, age at presentation, and family history of dissection. Mortality was 0.8% in low-risk, 6.1% in medium-risk, and 18% in highest-risk patients. The accuracy of this risk stratification should be confirmed in other series, mainly with the inclusion of sporadic TAA.

Therefore, while the defined gene mutations that predispose to disease development are still being elucidated, young adults with unexplained aortic disease or with positive family history of aortic diseases may raise the suspicion of a genetic etiology. Hypertension should be aggressively treated and controlled in individuals with familial TAA, including individuals with aneurysms and those at risk of developing aneurysms. Other cardiovascular risk factors, including smoking and hyperlipidemia, also should be addressed.

As in syndromic aortic diseases, some factors such as age, family history of aortic dissection, and perhaps a more rapid aortic growth rate during surveillance would identify the group of patients at higher risk who should undergo close imaging follow-up and more aggressive management. Results of the Sherrah et al. study show that adverse outcomes of familial NS-TAA are similar to those of Marfan syndrome (6). However, new studies are needed to confirm whether we can extend the current recommendations on the medical management and surgical indications of Marfan syndrome to the different types of NS-TAA diseases.

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