Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) registry predicting predictors for aortic dissection: a new thought around the corner?

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Submitted Aug 07, 2016. Accepted for publication Aug 10, 2016.
doi: 10.21037/jtd.2016.08.71

The multicenter prospective National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC) registry collects clinical and biological data from patients with aortic aneurysm and associated genetic conditions, including Marfan syndrome (MFS), Ehlers-Danlos syndrome, Loeys-Dietz syndrome, Turner syndrome, bicuspid aortic valve (BAV), and familial or premature (age <50 years) thoracic aortic aneurysm (TAA) (1). Patient enrollment began in November 2007 and the registry was born with the main objective to compare cross-sectional and longitudinal data on risk factors related to diagnosis, treatment, and outcome among groups of enrolled patients (1). Since then many important findings have emerged regarding the clinical characteristics and management of genetically-induced TAA and dissections (Table 1) (1-8).

In this last paper (9) from the GenTAC registry reported in the Journal of the American college of cardiology, the investigators set out to determine the relative risk for aortic dissection (AoD) in patients with TAA including those who previously underwent prophylactic TAA surgery, and then test the relationship between antecedent aortic size and subsequent AoD. BAV (39%) and MFS (22%) were the leading diagnoses among participants (n=1,991). Primary endpoint occurred in 1.6% (n=31) of patients and was assessed during a mean follow-up time of 3.6±2.0 years from baseline evaluation.

The present study raised three interesting points that offer insight for further considerations:

(I) MFS conferred greater relative risk for AoD (after 3 years of follow-up, the cumulative incidence was 6-fold higher in patients with MFS vs. the remainder of the population, log-rank P<0.001);

(II) Risk for AoD persisted even after TAA surgery (52% of affected patients had undergone previous aortic graft implantation) and it could occur within native aortic segments proximal or distal to prosthetic grafts;

(III) AoD can occur in at-risk patients even when aortic size is normal or minimally dilated (among patients with type A AoD, only 1 of 9 had an aortic diameter ≥5.0 cm in either the root or ascending aorta).

These findings confirmed that patients with genetically associated TAA remain at risk for AoD in the current era even after controlling for maximal aortic size and even after performing preventive surgical or medical treatments. Probably patients with TAA undergoing aortic grafting represent a high-risk phenotype in terms of intrinsic vascular properties that predispose them to aortic dilation and AoD. Unfortunately, mechanisms remain out of sight and thus many questions remain unanswered.

A recent paper coming from Yan et al. investigated the role of the structural cellular components of the aortic wall in the pathogenesis of AoD (10). They could demonstrate an overexpression of the octamer binding protein (Oct4) in the aortic media of AoD patients capable of inducing a phenotype switch of human aortic smooth muscle cells from the contractile to the synthetic type (10). This phenomenon may alter the normal biomechanical properties of aortic media facilitating pathological conditions such as AoD (11). In this way, investigating the mechanisms of AoD has gained an
increasing interest to reverse the prognosis of these patients.

Another unresolved issue highlighted in the present GenTAC study is the increased incidence of AoD observed in patients using beta-blockers compared with the remaining of the population (62% vs. 47%; P<0.001). Beta-blockers are presently considered to be first-line therapy in patients with MFS. However, their benefit is debatable and several observational studies including meta-analyses have reported conflicting results. Probably the small sample (31 patients experienced an AoD) and the lack on standardized medical therapy (50% of the entire population received a beta-blocker) could have influenced this finding; unfortunately, the authors do not provided any comment on this argument.

The only available randomized clinical trial comparing losartan with atenolol in children and young adults with MFS suggested no significant difference in the rate of aortic-root dilatation between the two treatment groups over a 3-year period (12). This topic could propel GenTAC investigators to further analyze medication patterns in order to prevent TAA and dissection.

The GenTAC database method has limitations, which the investigators discuss frankly in this paper. These regard image data collection performed using various imaging modalities and at different times across GenTAC sites but most importantly there is bias due to the registry enrollment which was skewed toward a more severe group of patients with genetically associated aortopathies with TAA.
In conclusion, AoD is a disease that has a catastrophic impact on a patient’s life. Unfortunately, it’s relative infrequency and overlapping clinical manifestations because missed diagnosis on delayed initial examination in more than 30% of patient (13). This paper provided us with clever hints to facilitate AoD diagnosis. The take home message in the author’s words is that “patients with genetically associated TAA remain at substantial risk for AoD despite state-of-the-art care and conventional imaging at experienced centers” and we add “…but mechanisms are still unknown”. Future endeavors to find genetic variants that might be associated with sporadic dissection could help to anticipate this catastrophic aortic syndrome.

Acknowledgements

None.

Footnote

Provenance: This is an invited Commentary commissioned by the Section Editor Lei Zhang (Department of Vascular Surgery, Shanghai, Second Military Medical University, Shanghai, China).

Conflicts of Interest: The authors have no conflicts of interest to declare.


References
