Editorial

Heritable aortic root aneurysms

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Introduction

Genetic discovery for heritable thoracic aortic disease (HTAD) is progressing at a brisk pace, leading to an increasingly personalized approach for these patients. Unlike abdominal aortic aneurysms that are predominantly driven by atherosclerosis and associated risk factors (age, smoking, hypertension), thoracic aortic aneurysms have a strong heritable predisposition with a 10-fold increased risk in first-degree relatives (1). Heritable aneurysms invariably involve the root and ascending thoracic aorta, whereas no monogenic disorders have been described for isolated descending or thoracoabdominal aneurysms. Genetic factors are increasingly informing the decision of when and how to operate on patients with aortic root aneurysms.

Genetic assessment for patients with root aneurysms

HTAD is comprised of single-gene disorders that are inherited primarily in an autosomal dominant manner with variable expression and incomplete penetrance. Although over 30 genes have been associated with thoracic aortic aneurysms and dissections (TAAD), careful curating identified 11 genes with definitive evidence supporting a gene-disease relationship for HTAD (2). These 11 genes include those encoding extracellular matrix proteins (*FBN1*, *LOX* and *COL3A1)*, proteins involved in TGFβ signaling pathway (*TGFBR1*, *TGFBR2*, *SMAD3* and *TGFB2)* and proteins involved in smooth muscle cell contraction (*ACTA2*, *MYH11*, *PRKG1* and *MYLK*).

The syndromic aortic disorders [including Marfan (MFS), Loeys-Dietz (LDS) and vascular Ehlers Danlos syndromes] present with extra-aortic manifestations that include the integumental, musculoskeletal, ocular, craniofacial and cardiovascular systems. There is considerable phenotypic overlap between disorders, and notably, pathogenic variants in *FBN1* or the TGFβ signaling genes may present without syndromic manifestations. As such, we recommend genetic testing with a multi-gene panel of the known HTAD genes for all patients with TAAD and one of the following: (I) syndromic features; (II) a 1st/2nd degree relative with TAAD, a peripheral/intracranial aneurysm, or sudden unexplained death at a young age; or (III) TAAD presenting at <60 years of age. A confirmed pathogenic variant should trigger gene-based management of the patient and cascade testing for at-risk relatives. Thoracic aortic imaging is recommended for all first-degree relatives of patients with TAAD and should be repeated at 5-to-10-year intervals.

Recent data from the Montalcino Aortic Consortium reported the risk of a first aortic event (elective aneurysm surgery or acute aortic dissection) among 7 HTAD genes (3). Smooth muscle cell gene variants were associated with a significantly higher risk of presenting with aortic dissection than TGFβ variants. Within the TGFβ signaling genes, a wide spectrum of aortic risk and systemic complications were observed, highlighting the importance of diagnosing individuals based on the clinical phenotype as well as the disease-causing gene.

Guidelines for surgical management of heritable root aneurysms

The 2022 American College of Cardiology/American Heart Association (ACC/AHA) aortic guidelines provided detailed recommendations for the management of patients with HTAD (4). Although size remains the best-established predictor for aortic dissection, many patients presenting with acute dissection have aortic diameters below the surgical threshold. In addition to considering the specific gene and variant involved, other factors such as pregnancy, hypertension, sex, body surface area, and biomechanical or structural properties of the aorta modulate the risk of dissection. As such, shared decision-making and a personalized approach balancing aortic and surgical risk must be considered.

With regards to diameter thresholds, MFS remains the prototypical condition, with root replacement recommended at ≥5.0 cm. Patients with high-risk features including rapid aortic expansion (≥3 mm/year), family history of aortic dissection, desire for pregnancy, or severe valvular regurgitation should be considered for earlier intervention (≥4.5 cm) by experienced surgeons. Recommended thresholds in LDS range from 4.0–5.0 cm, and depend on the specific gene/variant involved, the presence of severe syndromic features, and a family history of dissection. Specific consideration should be given to all patients with a family history of aortic dissection known to have occurred at small diameters or at a young age. For example, patients with *PRKG1* pathogenic variants may be offered elective surgical repair with little to no aortic enlargement because aortic dissections at normal aortic diameters can occur in these individuals. Patients with HTAD and no identified genetic cause should be treated with elective repair at 5.0 cm or earlier with high-risk features.

Surgical technique for hereditary root aneurysms

Elective surgery to replace the aortic root and ascending aorta has dramatically increased the life expectancy of patients with genetically triggered aneurysms. Although catastrophic proximal aortic events are mitigated, the risk of type B dissection remains and may even be increased following proximal replacement (5), leading to recommendations for lifelong β-blockade and avoidance of strenuous exercise. The entire ascending aorta should be replaced along with the root, and although selective replacement of the proximal arch may be reasonable, we do not consider a total arch replacement to be warranted in patients with HTAD undergoing elective surgery for root aneurysms.

Patients with HTAD undergoing elective root replacement should be referred to aortic surgeons expert in valve preservation. Although no randomized data exist, multiple single-center observational studies show a benefit in avoiding valve-related adverse events associated with prosthetic valves (6,7). It should be noted, however, that when studied in a prospective multicenter fashion, a higher incidence of aortic valve dysfunction was identified in patients with MFS who underwent valve-sparing procedures than those who underwent valve replacement (8). In this study, no differences were observed in survival, valve-related mortality, aortic valve reintervention, or bleeding, although longer follow-up is warranted.

Reimplantation of the aortic valve has been shown to be a more durable strategy than remodeling in patients with MFS (9,10). Although the literature is sparse, we suspect similar results would be observed for LDS and other conditions associated with annuloaortic ectasia. To achieve excellent long-term results following reimplantation of the aortic valve, it is crucial that surgeons address every component of the pathologic root, including correcting and stabilizing annuloaortic ectasia, excising all pathologic proximal aortic tissue and correcting any associated cusp abnormality.

Conclusions

Increasingly specific recommendations exist regarding management of aortic root aneurysms in patients with HTAD. Elective root replacement with reimplantation of the aortic valve is the preferred option for most patients with heritable root aneurysms. An improved understanding of genotype-phenotype correlations will ultimately lead to more precise gene- and variant-specific recommendations for surgical repair.

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Footnote

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