REVIEW

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Aortopathies: Etiologies, Genetics, Differential Diagnosis, Prognosis and Management

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ABSTRACT

Aortic root and ascending aortic dilatation are indicators associated with risk of aortic dissection, which varies according to underlying etiologic associations, indexed aortic root size, and rate of progression. Typical aortic involvement is most commonly seen in syndromic cases for which there is increasing evidence that aortic aneurysm represents a spectrum of familial inheritance associated with variable genetic penetrance and phenotypic expression. Aortic root and ascending aortic dimensions should be measured routinely with echocardiography. Pharmacologic therapy may reduce the rate of progression. Timing of surgical intervention is guided by indexed aortic size and rate of change of aortic root and ascending aorta dimensions. Lifelong surveillance is recommended.

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Aortopathy, including thoracic and abdominal aneurysms, is a major cause of morbidity and mortality in the US. Aortic aneurysms are the 15th leading cause of mortality in individuals >55 years of age.[1] The statistics relating to morbidity and mortality of aortic aneurysms identify a need to better understand the etiologies, genetics, diagnostic criteria, prognosis, and management of aortopathies. Improved imaging techniques in conjunction with current outcomes data for ascending and arch replacement surgery suggest we need a momentum shift toward increased screening and a lower threshold for elective surgery. The elective mortality for these interventions is in the 3.5% range, as opposed to 21% for emergent operations.[2] This manuscript explores the pathogenesis, genetics, diagnostic criteria, surveillance strategies, and treatment options for aortopathy needed to reduce the morbidity and mortality burden associated with this virulent disease.

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Figure 1 represents a case of Marfan syndrome and bicuspid aortic valve with challenging risk assessment and prevention management (**Table 1**). Differential diagnoses of ascending aortic aneurysm are listed in **Table 2**. This review addresses how to diagnose and manage thoracic aortopathies.

MARFAN SYNDROME

Marfan is a systemic connective-tissue, autosomal-dominant inherited disorder characterized by mutations in the fibrillin-1 gene (FBN1). Its prevalence is approximately 1 in 5000 individuals. There is no sex, racial, or ethnic predilection, and one third of cases present without previous family history.[3] Despite effective treatment of aortic root disease, cardiovascular morbidity remains high due to arrhythmia, heart failure, complications at distal sites of the aorta, and valvular dysfunction.[4] Without aortic root surgical therapy for progressive aortopathy, Marfan patients rarely survive their 40s.

Aortic disease in Marfan classically manifests as an ascending aortic aneurysm involving the sinuses of Valsalva and the tubular portion of the ascending aorta, producing "pear-shaped" annuloaortic ectasia, in which both the aortic annulus and ascending aorta are enlarged in a conical Erlenmeyer flask-like shape.

Pathogenetics

Approximately 1000 different mutations involving FBN1 gene have been identified, without correlation between the specific type of FBN1 mutation and the multiple clinical phenotypes. Severe cardiovascular involvement is often associated with mutations in the middle region (exons 24-32) of the locus.[5] The same family sharing a unique FBN1 mutation may have heterogeneous phenotypic age of onset and degree of Marfan-associated manifestations. Classically, FBN1 mutations result in dysregulation of transforming growth factor-beta (TGF-β), weakened and disordered elastic fiber formation in the aortic wall, and disruption of the microfibril network connecting the elastic lamellae to the adjacent interstitial cells.[6]

CLINICAL SIGNIFICANCE

- Ascending aortic aneurysm can be inherited or sporadic, but different etiologies may represent a disease spectrum rather than discrete entities.
- After initial diagnosis, establish rate of progression with serial imaging (preferably echocardiography) every 6 months (minimum: 3 serial studies). Subsequent annual monitoring of stable patients is recommended. Imaging above sinotubular junction is important.
- Disease is recurrent; surgical intervention does not negate need for routine surveillance.
- Family members should be screened.

Diagnosis

Diagnosis of Marfan syndrome continues to depend on clinical features based on the Ghent diagnostic criteria.[7-9] The criteria support a uniform approach to diagnosis, encompassing a multidisciplinary approach involving cardiac, orthopedic, ophthalmologic, and genetic evaluation/testing. Likelihood of finding a pathological mutation in FBN1 in patients with Marfan using Ghent criteria approximates 95%.[8]

The cardiovascular manifestations of this mutation[10] are a major cause of morbidity and mortality in Marfan patients (**Table 3**). Aortic dissection is the most common cause of mortality; 50% of patients <40 years old who remain undiagnosed die from aortic dissection, with a steep increase during adolescence. Alternatively, treated patients can have near-normal life expectancy.[9] Features associated with risk for dissection are listed in **Table 4**.[11-13]

Imaging Strategy

Annual transthoracic echocardiography is standard surveillance in adults with Marfan. Upon initial diagnosis of Marfan, the patient should have 3 echocardiograms at 6-month intervals to establish the rate of progression of dilatation. Once growth rates are established to be stable, annual monitoring of aortic root dimensions is recommended. Echocardiographic measurements should include: 1) transsinus diameter, 2) sinotubular junction, 3) proximal and middle ascending aorta, and 4) aortic arch (**Figure 2**). Aortic size in isolation is not helpful in surgical decision-making. Z-scores (SDs from normal) in children and aortic size indexed to body surface area in adults are indices that facilitate surgical decision-making[14-17] in patients with aortopathy. Echocardiographic structural and Doppler tissue physiologic assessment of aortic wall mechanics helps predict risk of aortic dissection/rupture (**Table 5**).

Pharmacologic-assisted Management

Beta-blocker therapy is the most studied drug treatment in the management of Marfan aortopathy.[18] More recently, treatment with angiotensin-converting enzyme inhibitors has been advocated.[19] Compared with atenolol, enalapril has been shown to improve aortic distensibility, reduce arterial stiffness, and result in a smaller root diameter.[19] Angiotensin receptor blockers are evolving as a potential treatment option.[20,21] Circulating TGF-β concentrations are elevated in Marfan patients and decrease after treatment with losartan, beta blockers, or both, suggesting TGF-β has a prognostic implication in Marfan, and drug therapy may alter the phenotypic expression of the disease.[22]

Sleep Apnea

Thirty percent of patients with Marfan have obstructive sleep apnea.[23,24] Obstructive sleep apnea absent treatment is associated with significant alteration in nocturnal intrathoracic pressure that could potentially promote more rapid progressive aortic root dilatation. It has been demonstrated that half of all episodes of apnea in patients with Marfan are central rather than obstructive.[25] Appropriate treatment of sleep apnea in patients with Marfan is essential to prevent the multimorbidity of atrial fibrillation, heart failure, and diabetes.[26]

Surgical Intervention

Current indications for aortic root surgical intervention in patients with Marfan[27] are listed in **Table 6**. In Marfan patients with aortic root diameter <50 mm and preserved aortic valve function, an aortic valve-sparing operation should be considered. Surgical evaluation of the aortic valve leaflets (for fenestrations) and leaflet/root geometry is important. Valve-sparing operations have similar outcomes to valve replacement surgery.[28] Women considering precounseled pregnancy should be offered surgery if the aortic root is >4.5 cm before conception, with consideration for valve-sparing aortic root surgery or a bioprosthetic composite graft. Aortic root surgery in children should be considered when the aortic dimension approaches 2 SDs above normal.[14,15]

Elective aortic root replacement in Marfan patients is considered for some individuals in whom the aorta is 4.5−5 cm in the clinical setting of accelerated aortic dimension