Cardiovascular Management of Marfan Syndrome

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Key words: Marfan syndrome, fibrillin-1 gene, ascending aorta, beta-blockade, prophylactic aortic root surgery

IMAJ 2008;10:182–185

In 1896, at a meeting of the Medical Society of Paris hospitals, Antoine Marfan presented a 5 year old girl with abnormalities of the skeletal system and elongation of the long bones and fingers (arachnodactyly). In 1914 the disorder was given official recognition as Marfan syndrome, based on skeletal abnormalities and ectopia of the lenses. In 1943, a description of a dilated aortic root as well as dissection was reported for the first time [1].

Marfan syndrome is an autosomal dominant connective tissue disorder affecting mainly the cardiovascular system, eyes and skeleton. With regard to its epidemiology, the incidence is approximately 1:5000–10,000; about 25% of cases have no family history and their syndrome is the result of sporadic mutation [2-4]. Marfan syndrome affects males and females equally and appears to be distributed equally among all races and ethnic groups.

Diagnosis by nosology

The Berlin Nosology of Heritable Disorders of Connective Tissue was published in 1986. The Berlin nosology has been replaced by the Ghent nosology (1996) which codifies the criteria for the diagnosis of Marfan syndrome [5] [Table 1].

Regardless of how crippling the skeletal deformities may be, the predominant factor determining survival is cardiovascular involvement of the ascending aorta. In fact, the degree of the skeletal deformity does not necessarily correlate with the severity and extent of the cardiovascular disease. Indeed, a patient might present with mild skeletal deformities and severe cardiovascular disease, or vice versa.

Marfan syndrome almost always results from a mutation in the fibrillin-1 gene on chromosome 15 (it was limited to an unknown gene on chromosome 3 in a single family). Two decades ago when fibrillin abnormalities were reproduced in Marfan syndrome, the general feeling in the profession was that this was an ironclad criterion. Unfortunately this theory did not bear fruit since very few mutations of fibrillin-1 have been observed more than once, whereas more than 400 causative mutations have been found in almost as many as the families studied. Fibrillin-1 mutations have also been found in Marfan-related disorders. Nevertheless, to date the most reliable prognostic information remains the patient's own family history [6,7].

In this context, it should be noted that the rate of mutation of the fibrillin gene appears to be related to the age of the patient's father: older fathers are more likely to have new

Table 1. Ghent criteria for the diagnosis of Marfan syndrome

System	Major criterion	Involvement
Skeletal	At least four of the following features:	Two of the major features, or one major feature and two of the following:
	• Pectus carinatum • Pectus excavatum requiring surgery • ULSR < 0.86 or span, height > 1.05 • Wrist and thumb signs • Scoliosis > 20° or spondylolisthesis • Reduced elbow extension (< 170°) • Pes planus • Protrusio acetabulae	• Pectus excavatum • Joint hypermobility • High palate with dental crowding • Characteristic face
Ocular	Lens dislocation (ectopia lentis)	Flat cornea Increased axial length of globe (causing myopia) Hypoplastic iris or ciliary muscle (causing decreased miosis)
Cardiovascular	Dilatation of aortic root Dissection of the ascending aorta	Mitral valve prolapse Dilatation of the pulmonary artery, below age 40 Calcified mitral annulus, below age 40 Other dilatation of dissection of the aorta
Pulmonary	None	Spontaneous pneumothorax Apical blebs
Skin/ integument	None	Striae atrophicae
Dura	Lumbosacral dural ectasia	None
Genetic findings	Parent, child or sibling meets these criteria independently Fibrillin-1 mutation known to cause Marfan syndrome Inheritance of DNA marker haplotype linked to Marfan syndrome in the family	None

ULSR = upper to lower segment ratio

mutations appearing in chromosome 15 [8]. The most severe end of the phenotypic spectrum of this disorder is neonatal Marfan syndrome. This group of patients is usually diagnosed at birth and their life expectancy is little more than a year. The infants usually die of congestive heart failure rather than aortic aneurysmal disease, the most frequent cause of morbidity and mortality in the classical adult form [9,10].

Life expectancy, determined by the severity of the cardiovascular involvement, has changed as the medical community has come to grips with this condition, especially its implementation of the following management approaches:

- Beta-blockade, which reduces the rate of aortic dilatation in some patients
- Prophylactic aortic root surgery, which several recent series have shown to be superior to emergency surgery for dissecting aneurysm
- The timing of prophylactic surgical intervention, which depends on aortic diameter and its rate of dilatation
- Commitment of both doctor and patient to lifelong medical treatment, as well as aortic surveillance and regular aortic follow-up.

Differential diagnosis

Most common is mitral valve prolapse with skeletal (mainly thoracic) abnormalities with other features characteristic of Marfan. Fibrillin-1 mutation was described in one case.

MASS syndrome is a disorder manifesting such Marfan features as myopia, mitral valve prolapse, aortic dilatation, skin involvement, ectopia lentis and mild "stable" aortic dilatation. This disorder has a far better prognosis than Marfan and should be addressed differently.

Autosomal dominant lens ectopia with skeletal changes, fibrillin-1 mutation but with no cardiac involvement.

Rare syndromes to be differentiated are: a) Lujan-Fryns syndrome (mental retardation with marfanoid features); b) Shprintzen-Goldberg syndrome (craniosynostosis with fibrillin-1 mutation, considered a variant of Marfan syndrome); and c) Beals syndrome (congenital contractual arachnodactyly, with fibrillin-2 mutation and ear abnormalities). This syndrome does not usually affect the aorta or the eyes [11,12].

Histopathology

The aorta of patients with Marfan is characterized histologically by elastic fiber fragmentation and disarray, paucity of smooth muscle cells, and deposition of collagen and mucopolysaccharides between the cells and the media. The molecular basis for the elastic fiber abnormality is the fibrillin disorder, an important component of the elastic microfibril.

Laboratory findings

Fibrillin is a 350 kD glycoprotein, synthesized as a 375 kD precursor that is processed and secreted into the matrix encoded by the fibrillin-1 gene, which maps to chromosome 15q21.1.

Mutation in another fibrillin gene (fibrillin-2, mapping to chromosome 5q23-31) causes Beals syndrome. With current techniques of diagnosis according to the Ghent criteria, fibrillin-1 mutations can be detected in about 66% of Marfan patients. A wide variability in severity has been documented with different mutations, even in the same codon, causing either severe neonatal Marfan syndrome or classical adult Marfan syndrome.

Aortic elastic fiber degeneration leads to reduced distensibility in response to pulse pressure wave, which results in increased stiffness of the aorta, tears and dilatation. Whereas the normal aorta gradually dilates and stiffens with age in Marfan, those changes are more pronounced at any age and can be detected by echocardiography or gated magnetic resonance imaging [12].

Complications in Marfan syndrome

The cardiac complications include

- Aortic root dilatation
- Aortic valve incompetence
- Risk of aortic rupture
- Myocardial infarction if an aortic root dissection occludes the coronary ostia
- Mitral valve prolapse and regurgitation
- Left ventricular dilatation
- Cardiac failure and pulmonary artery dilatation.

Marfan syndrome mortality from complications of aortic root dilatation decreased from 70% in 1972 to 48% in 1995. Associated with the increased medical and surgical intervention, life expectancy increased from a mean (± SD) age at death of 32 (± 16) years in 1972 to 45 (± 17) years in 1998.

The risk factors for aortic dissection are increased aortic diameter, extent of aortic dilatation, rate of aortic dilatation, and family history of aortic dissection [13,14] [Figure 1].

Management

Studies in turkeys prone to aortic dissection showed improved survival following treatment with propanolol. A randomized trial

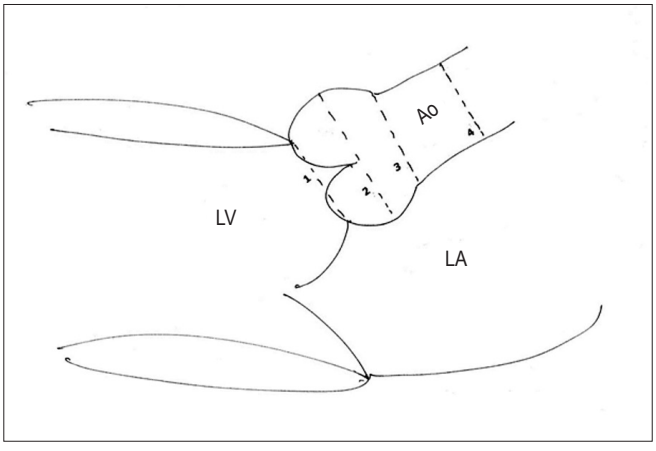

Figure 1. Schematic diagram of the ascending aorta as demonstrated on echocardiography with parasternal long-axis view. The broken lines represent critical landmarks that effect mainly the surgical approach. 1 = the annulus, 2 = sinus of Valsalva, 3 = sinotubular junction, 4 = ascending aorta.

of propanolol treatment in 70 adolescent and young adult Marfan patients demonstrated a reduced rate of aortic dilatation and fewer aortic complications in the treatment group. Atenolol treatment in 113 patients yielded similar effects [15].

Beta-blockade with propanolol [16], atenolol or metoprolol increased aortic distensibility and reduced aortic stiffness and pulse wave velocity. Those who responded to beta-blockade tended to have smaller aortic diameters (< 4 cm in one study), in keeping with other studies suggesting that the reduction in the rate of aortic dilatation with beta-blockade is greatest in younger patients [17,18].

Cardiac complications, however, are rare in young patients with Marfan syndrome receiving medical therapy and under close clinical follow-up. Sudden death still occurs and is more common in patients with a dilated left ventricle. Left ventricular dilatation may predispose to alterations of repolarization and fatal ventricular arrhythmias [19]. An exception to this finding is a recent study that followed 63 children with Marfan syndrome from age 9 (± 4.0) years with echocardiograms 18–36 months apart. The study suggested that beta-blocker therapy does not significantly alter the rate of aortic dilatation in children and thus urged reassessment of the recommendation of lifetime beta-blocker therapy starting in childhood [20].

Calcium antagonists or angiotensin-converting enzyme inhibitors have been suggested, but no reported clinical trials have been performed to confirm the benefit of these drugs. Theoretical reasons suggest considering ACE inhibitors or angiotensin II receptor blockers. Vascular muscle cell apoptosis has been implicated in the cystic medial degeneration seen in the Marfan aorta and both types of drug have been shown to inhibit vascular smooth muscle cell apoptosis in cultured Marfan aortic media cells. To date, however, we are not aware of phase III clinical studies proving any of those medications superior to beta-blockers in either adolescents or adults [21].

Marfan syndrome and pregnancy

The risk of aortic dissection in pregnancy is increased, possibly due to inhibition of collagen and elastin deposition in the aorta by estrogen, and the hyperdynamic hypervolemic circulatory state of pregnancy. Gestational hypertension and preeclampsia may increase the risk of aortic rupture. Nine of 83 women (11%) had severe complications, mostly aortic rupture. Cardiovascular complications appear more likely if the aortic root is larger than 4 cm. Women with Marfan syndrome and an ascending aorta ≥ 4.0 should be advised against pregnancy [22].

Marfan syndrome and sports

Athletes with Marfan syndrome can participate in low and moderate static/low dynamic competitive sports if they do not have one or more of the following: a) aortic root dilatation (i.e., transverse dimension ≥ 40 mm) in adults; b) moderate to severe mitral regurgitation; or c) family history of dissection or sudden death in a Marfan relative. Athletes should have an echocardiographic measurement of aortic root dimension repeated every 6 months. Athletes with aortic root dilatation (dimension ≤ 40 mm) prior to surgical aortic root reconstruction, dissection of aorta or other artery, moderate to severe mitral regurgitation, or family history of dissection or sudden death can participate in low intensity competitive sports only. Finally, athletes with familial aortic aneurysm or dissection, or congenital bicuspid aortic valve with any degree of ascending aortic enlargement should not participate in sports that involve the potential for bodily collision [23].

Presurgical management

Adoption of the 2006 American Heart Association/American College of Cardiology guidelines [24] for the management of bicuspid aortic valve with dilated ascending aorta could most appropriately be applied to patients with Marfan syndrome and dilated ascending aorta as follows:

Class I

- Patients with known Marfan syndrome should undergo an initial transthoracic echocardiogram to assess the diameters of the aortic root and ascending aorta.
- MRI or computed tomography is indicated at least once to rule out dilatation along the descending aorta or when morphology of the aortic root or ascending aorta cannot be assessed accurately by echocardiography.
- Diameter > 4.0 cm should undergo serial evaluation of aortic root/ascending aorta size and morphology by echocardiography, MRI or CT on a yearly basis.
- Surgery to repair the aortic root or replace the ascending aorta is indicated if the diameter of the aortic root or ascending aorta is > 5.0 cm or if the rate of increase in diameter is ≥ 0.5 cm per year.
- Special attention should be paid to patients who have a family history of dissecting aneurysm.

Class IIa

- It is reasonable to prescribe beta-adrenergic blocking agents to patients with Marfan syndrome and dilated aortic roots (diameter > 4.0 cm) who do not have moderate to severe aortic regurgitation.
- MRI or CT is feasible in patients with Marfan syndrome when aortic root dilatation is detected by echocardiography to further quantify severity of dilatation and involvement of ascending aorta.

Conclusion

Of particular interest is the phenomenon that as Marfan patients survive longer due to recent advances in aortic and aortic valve surgery, reoperation for new aneurysms developing elsewhere in the arterial tree is becoming common. Since 70% of post-surgical patients developed second aneurysms, continuation of long-term beta-blockade after surgery is of critical importance [25].

ACE = angiotensin-converting enzyme

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