Tzu Chi Medical Journal 2022; 34(1): 44-48

Review Article

An update of medical care in Marfan syndrome

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Abstract

Marfan syndrome (MFS), a multisystemic connective disorder, caused by fibrillin 1 gene mutations with autosomal dominant inheritance. The disease spectrum is wide and the major causes of death are related to aortic root aneurysm or dissection. The purposes of medical treatment are to reduce structural changes in the aortic wall and slow aortic root dilatation. Advance in medical researches have provided new insights into the pathogenesis of disease and opened up new horizons for treatments. Several medications such as angiotensin II type I receptor blockers, β-blockers, angiotensin-converting enzyme inhibitors, calcium channel blockers, tetracyclines, and statins have been studied for the purpose. Currently, the life expectancy of Marfan patients improves significantly and is closes to the general population with proper treatment. In this article, we review and update the medical treatments for patients with MFS.

Keywords: *Angiotensin-converting enzyme inhibitor, Angiotensin II receptor blocker, Aortic dissection, Beta-blockers, Marfan syndrome*

Submission : 30-Apr-2020
Revision : 11-Jun-2020
Acceptance : 25-Jun-2021
Web Publication : 10-Sep-2021

Introduction

Marfan syndrome (MFS) is one of the most common inherited connective tissue disorders caused by fibrillin-1 (FBN1) gene mutation. It exhibits complete penetrance but with highly variable expressions [1,2]. The clinical manifestations involve the cardiovascular, ocular, and musculoskeletal systems with highly variable severity. Cardiovascular collapse is the main cause of death due to aortic dissection or rupture [2-5]. Over the past 3 decades, the life expectancy of MFS patients has increased significantly because of advanced applications of genetic screening, medical and surgical management [6-8].

Fibrillin-1, a major component of elastin-associated microfibrils, is a glycoprotein that is found throughout the extracellular matrix. Fibrillin-1 has been shown to regulate transforming growth factor β (TGF-β) activation by sequestering it in association with specific latent TGF-β binding proteins [9,10]. Loss of fibrillin-1 may then lead to over-release of TGF-β, which contributes to matrix metalloproteinases (MMP) activation and extracellular matrix degeneration leading to aortic dissection or even rupture [11,12].

The clinical presentations of MFS become more apparent with increasing age; it is really a challenge to make an accurate diagnosis especially in children. The current diagnosis of MFS relies on the 2010 revised Ghent criteria [Table 1], which put more weight on aortic root aneurysm and ectopia lentis as well as FBN1 mutation and family history of MFS [13]. A new scoring system with a maximum score of 20 has been designed for other system's features and a score ≥7 is considered positive systemic involvement [Table 2]. To make a diagnosis of MFS, patients should meet the following conditions: (1) In the absence of family history of MFS, patients with aortic root dilatation/dissection combined with ectopia lentis, or a causative FBN1 mutation, or a systemic score ≥7. For those without aortic root dilatation/dissection, MFS will be diagnosed when they have both ectopia lentis and a causative FBN1 mutation. (2) In the presence of family history of MFS, patients with ectopia lentis, or aortic root dilatation/dissection, or a systemic score ≥7, could be diagnosed as MFS [Table 1].

Three alternative diagnoses were defined to differentiate from MFS. (1) Ectopia lentis syndrome (ELS) indicated patients with ectopia lentis and an FBN1 mutation not known to cause aortic disease or without FBN1 mutation, regardless of systemic score ≥7. (2) MASS phenotype (myopia, mitral valve prolapse, borderline aortic root diameter, skeletal findings, and striae) indicated those without ectopia lentis but mild cardiac (aortic root Z score <2) and systemic features (systemic

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Access this article online

Quick Response Code:

Website: www.tcmjmed.com

DOI: 10.4103/tcmj.tcmj_95_20

How to cite this article: Chiu HH. An update of medical care in Marfan syndrome. Tzu Chi Med J 2022; 34(1): 44-8.

Table 1: Revised Ghent criteria for the diagnosis of Marfan syndrome and related disorders

MFS
In the absence of family history of MFS
Aortic root diameter *Z** ≥2 or dissection AND ectopia lentis
Aortic root diameter *Z** ≥2 or dissection AND a causative FBN1 mutation†
Aortic root diameter *Z** ≥2 or dissection AND systemic score≥7‡
Ectopia lentis AND a causative FBN1 mutation†
In the presence of family history of MFS
Ectopia lentis
Systemic score≥7‡
Aortic root dilatation (*Z** ≥2 in adults≥20 years; Z* ≥3 in individuals<20 years)
ELS
Ectopia lentis with or without systemic score≥7‡ AND an FBN1 mutation† not known to be associated with aortic disease or without FBN1 mutation†
MASS phenotype (myopia, mitral valve prolapse, borderline aortic root diameter, skeletal findings and striae)
Aortic root diameter *Z** <2 AND systemic score≥5‡ with at least one skeletal feature without ectopia lentis
MVPS
Mitral valve prolapse AND aortic root diameter *Z** <2 AND systemic score<5‡ without ectopia lentis

**Z*: A Z score, also called a standard score, is a measure of how many standard deviations above or below the population mean a raw data is, †FBN1: A causative FBN1 mutation means an FBN1 mutation was known to be associated with aortic disease, ‡Cobb angle at least 20°. MFS: Marfan syndrome, ELS: Ectopia lentis syndrome, MVPS: Mitral valve prolapse syndrome, FBN1: Frbrillin-1, *Z*=Z score, MASS: Myopia, mitral valve prolapse, borderline aortic root diameter, skeletal findings and striae

Table 2: Systemic scoring for marfan syndrome

Systemic feature	Score
Wrist AND thumb sign	3
Wrist OR thumb sign	1
Pectus carinatum	2
Pectus excavatum	1
Chest asymmetry	1
Hindfoot deformity	2
Plain pes planus	1
Pneumothorax	2
Dural ectasia	2
Protrusio acetabuli	2
Reduced upper segment/lower segment* AND increased arm/height† AND no severe scoliosis‡	1
Scoliosis or thoracolumbar kyphosis‡	1
Reduced elbow extension	1
Facial features (3/5) Dolichocephaly, enophthalmos, malar hypoplasia, downslanting palpebral fissures, retrognathia	1
Skin striae	1
Myopia>3 diopters	1
Mitral valve prolapse	1

*The lower segment is the distance from the top of the symphysis pubis to the floor in standing position; the upper segment is the height minus the lower segment. In adult, the ratio<0.85 for white adult, <0.78 for black, but no data have been associated in Asians, in children, the ratio <1 for age 0-5 years, <0.95 for 6-7 years, <0.9 for 8-9 years, and<0.85 for age above 10 years, †>1.05, ‡Cobb angle at least 20°. Maximum total score: 20, score ≥7 indicate positive systemic involvement

score ≥5 with at least one skeletal feature). (3) mitral valve prolapse syndrome indicated patient without ectopia lentis but mitral valve prolapse, borderline aortic root diameter (Z score <2), and systemic score <5 [Table 1].

Several connective tissue disorders having marfanoid phenotype and the risk of aortic dissection result from other genes mutation [13,14]. Loeys-Dietz syndrome, also known as MFS type 2 (MFS2), caused by TGFBR1, TGFBR2, TGFB2, TGFB3, or SMAD3 genes mutation. Sphrintzen-Goldberg syndrome caused by SKI or rarely FBN1 genes mutation. Ehlers-Danlos syndrome (vEDS) caused by COL3A1 gene mutation in vascular type, TNXB gene mutation in hypermobility type, PLOD1 gene mutation in kyphoscoliotic type, and COL5A1/COL5A2 gene mutation in classic type. Familiar thoracic aortic aneurysm and dissection caused by ACA2, MYLK, PRKG1, MYH11, MFAP5, and MAT2A genes mutation. At present, the medical care for those connective tissue disorders follows the treatment principles of MFS.

Treatment for cardiovascular manifestations

Clinical care for patients with MFS needs a multidisciplinary team for comprehensive management, including cardiologist, geneticist, orthopedist, ophthalmologist, cardiothoracic surgeon, and obstetrician. The classical standards imply: (1) diagnosis confirmation and medical treatment for aortic protection; (2) prophylactic aortic root surgery; (3) serial imaging follow-up of the aorta; (4)

endocarditis prophylaxis; (5) lifestyle modification and avoid moderate intensity of exercise; and (6) counseling on pregnancy [15,16].

The most life-threatening complication of MFS is aortic dissection or rupture, especially in those without treatment. The medical and surgical strategies for MFS patients are aimed to prevent cardiovascular events.

Pharmacological treatment

Beta-blockers

Many studies reported that β-blockers had the effect in slower aortic root growth rate and fewer cardiovascular complications from its negative chronotropic and inotropic effects, which can reduce hemodynamic stress on the aortic wall [17-19]. It was first proposed by Halpern *et al*. in 1971[20] and is regarded as the first-line prophylaxis for MFS. However, several studies showed heterogeneous results and even suggested that the β-blockers might worsen aortic elasticity, especially in those with aortic root diameter >40 mm in end-diastolic phase or increased body weight [21-23]. Salim *et al*. reported that during a lifetime, the aortic root growth rate reached its peak at 6 to 14 years of age [19]. Hence, β-blockers are generally initiated once MFS is diagnosed, especially those before puberty, and suggest lifelong treatment, even in patients who received aortic surgery [24,25]. The resting heart rate was suggested to keep around 60-70 bpm in adult, and less than 100 bpm during submaximal exercise in adult or teenage, and less than 110 bpm in children [15,24]. Currently, propranolol or atenolol are the most widely used β-blockers for pediatric MFS with well tolerance [24,25].

Angiotensin II type I receptor blockers

In mouse models of MFS studies suggest that FBN1 gene mutations might activate TGF-β signaling and resulted in fragmentation and disarray of elastic fiber in aortic media, which would lead to the formation of aortic aneurysms [26,27]. Losartan, an Angiotensin II type I (AT1) receptor blocker, has been proved to effectively reduce aortic root dilatation and lung tissue degradation in an MFS mouse model by blocking the AT1 receptor and inhibiting the subsequent TGF-β signaling [28,29]. Followed studies showed that losartan was safety and effective in MFS patients [30-33]. Losartan treatment reduced aortic root and arch dilatation rates in operated or unoperated adult MFS [32]. The efficacy was related to longer treatment duration and earlier treatment age, but not related to the type of FBN1 mutation or clinical presentation [33].

However, several randomized trials comparing losartan and atenolol treatment over 3 years for children and adults MFS with aortic root dilatation reported that there was no significant difference in aortic root growth rate [34-36]. Even so, the aortic root Z score of each group decreased significantly over time, especially in younger patients [34]. Several clinical trials reported that losartan add-on β-blockers therapy provides better protection against aortic root dilatation than β-blockers alone in adults and children MFS [30-32]. Except losartan, another AT1 receptor blocker, irbesartan was reported to reduce the rate of aortic dilatation in both children and young adult MFS [37]. Therefore, losartan or other AT1 receptor blockers seem to have an equivalent effect to β-blockers and could be a safe alternative in the management of MFS. Currently, a meta-analysis reported that only-AT1 receptor blocker therapy is not inferior to only-β-blocker therapy for cardiovascular protection in MFS. Besides, the outcomes of AT1 receptor blocker-plus-β-blocker therapy seemed to be favorable than only-β-blocker therapy [38].

Angiotensin-converting enzyme inhibitor

Angiotensin II plays an important role in aortic aneurysms formation which is upregulated through activation of ACE and chymase-dependent pathways [39]. ACE inhibitors are reported to improve aortic distensibility and slow the progression of aortic aneurysm in atherosclerosis studies [39,40]. The effects of ACE inhibitors are through blood pressure control and may reduce apoptosis of aortic wall by blocking the angiotensin II type II receptor [24]. Some small clinical studies indicated that ACE inhibitors could reduce both aortic stiffness and aortic root diameter more than β-blockers therapy in patients with MFS [41,42]. However, other studies showed a limited effect of ACE inhibitors on aortic growth [43,44]. Large prospective trials are recommended for further evaluation.

Calcium channel antagonists

Calcium channel antagonists have been proven to promote vascular remodeling and improve endothelial function, and are considered an alternative if β-blockers are intolerable. However, the clinical evidence of safety and efficacy in MFS are limited [18,44]. In a study of MFS mice, it was even noticed that calcium channel antagonists would accelerate aortic aneurysm growth, dissection, and early mortality [45]. The mechanism may be through increase TGF-β signaling cascades via activation of AT1 receptors mediated - ERK1/2 pathway. Therefore, calcium channel antagonists should be used with caution in patients with syndromic inherited thoracic aortopathy or congenital heart disease [45].

Statins

Statins, one HMG-CoA reductase inhibitor, are a class of cholesterol-lowering agent and primary used in treatment or prevention of atherosclerosis. In clinical studies of abdominal aortic aneurysm, statins are reported to prevent progressive aortic root dilatation and decreased long-term mortality by inhibition of Ras-dependent ERK (Extracellular Signal-Regulated Kinase) pathway, leading to decrease the matrix MMP -9 production [46,47]. Similar findings were also reported in Marfan mouse models as well as preserved elastin volume in the aortic wall [48,49]. Although statins are generally safe, some important adverse effects such as an increased risk of diabetes mellitus, liver dysfunction, myalgia, and rarely rhabdomyolysis should be cautioned and monitored. Further clinical trials with large scale are warranted for efficacy and safety evaluation.

Tetracyclines

Doxycycline, a tetracycline, is reported to delay aortic aneurysm rupture by suppressing the expression of MMP-2,9 in mice models of MFS [50,51]. In a small human study, doxycycline was implicated to decrease the growth rate of

abdominal aortic aneurysm [52]. Nevertheless, the clinical evidence in patients with thoracic aortic aneurysm are still quite limited.

Endocarditis prophylaxis

The dental problems are common to MFS patients due to high-arched palate with crowded teeth. Hence, regular intraoral monitoring and subacute bacterial endocarditis prophylaxis are advised for MFS patients with valvular insufficiency [24].

Conclusion

Patients with MFS require multidisciplinary care including closely monitor the aortic dimension and heart function, strictly control cardiovascular risk factors, timely medication, and prophylactic surgery. Summarizing currently available evidences, β-blockers are recommended in patients with MFS-associated aortoapthy. AT1 receptor blockers, especially losartan, could be alternative choices. However, combination therapy with β-blockers and losartan may provide more cardiovascular protection in patients with MFS.

With the advances in pathogenesis of aortopathies and genomic medicines, treatment has entered the era of personalized and precision medicine. We wait for the results from many ongoing trials in near future and anticipate the treatment strategies might shift from current phenotype/syndrome considerations to genotype/pathogenesis considerations.

Financial support and sponsorship

This study was partially supported by the Ministry of Science and Technology (MOST 108-2314-B-303-020-MY3).

Conflicts of interest

There are no conflicts of interest.

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