



Importance of Early Detection and Cardiovascular Surgical Intervention in Marfan Syndrome

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ABSTRACT

Marfan syndrome is an autosomal dominant connective tissue disorder that affects multiple systems, including the skeletal, ligamentous, oculofacial, pulmonary, abdominal, neurological, and cardiovascular systems. Cardiovascular complications, which involve the aorta and aortic valve, contribute most significantly to patient morbidity and mortality. A literature review was conducted on pathophysiology of the disease and recommendations for early diagnosis and treatment. Diagnosis largely relies on clinical features and a thorough history. Echocardiogram is used for monitoring aortic abnormalities and disease progression. Aortic valve-sparing surgery is indicated in any valvular abnormality and in patients with a murmur. Aortic root replacement is indicated prophylactically in women who want to give birth with diameters greater than 40 mm, anyone with a diameter greater than 50 mm, and progressive dilatation of greater than 5 mm per year. Medical management involves antihypertensive therapy. It is imperative for all health care providers to understand the clinical features, progression, and management of Marfan syndrome to appropriately care for their patients. Ensuring regular follow-up and adherence to medical and surgical prophylaxis is essential to patient well-being. **Key words:** cardiovascular, genetics, Marfan syndrome

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MARFAN SYNDROME has unique implications in emergency care. Marfan syndrome occurs in one in every 5,000 individuals (Yip & Sawatzky, 2014).

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Unfortunately, the literature is devoid of current updates on evaluation and management of the syndrome. This article provides a review of evidence-based practice, current evaluation, and management of Marfan syndrome.

Marfan syndrome is caused by a mutation of the fibrillin gene (*FBN1* gene) located on chromosome 15, which encodes for microfibrillar glycoprotein fibrillin (Canadas, Vilacosta, Bruna, & Fuster, 2010). Reduced or abnormal fibrillin-1 leads to tissue weakness, increased transforming growth factor beta (TGF- β) signaling, loss of cell-matrix interactions, and different phenotypic manifestations of Marfan syndrome (Canadas et al., 2010). Abnormal activation of TGF- β stimulates inflammation and fibrosis and leads to dysregulation of matrix homeostasis (Keane & Pyeritz, 2008). Defective connective tissue affects multiple systems of the body, with the most devastating affects being within the cardiovascular system. Ongoing destruction of the elastic and collagen layers and medial degeneration result in progressive dilatation of the aorta, as well as a predisposition to aortic dissection from the loss of appropriate medial layer support (Keane & Pyeritz, 2008). Loss of elasticity in the media also results in progressively increased aortic stiffness (Keane & Pyeritz, 2008). Although studies prove that a mutation in *FBN1* gene leads to manifestation of Marfan syndrome, no simple laboratory test is available to support the diagnosis, and other conditions may also have a fibrillin defect (Jain & Pandey, 2013). The diagnosis of Marfan syndrome relies on meticulous physical examination, clinical symptoms, family history, and investigation of involved organ systems (Jain & Pandey, 2013).

CLINICAL FEATURES

The variable severity in the clinical presentation of Marfan syndrome is determined by the expression of the fibrillin and the *FBN1* gene mutation (Dean, 2007). Typically Marfan's features include a thin body type with tall stature, arachnodactyly, scoliosis or kyphosis, ligamentous laxity, flat feet, and/or lumbosacral dural ectasia (The Marfan Foundation, 2014a).

Facial features include dolichocephaly (elongated face), down-slanting palpebral fissures, high and arched palate, dental crowding, and iridodonesis (vibration of the iris with eye movement due to lens dislocation) (Leoni, Bowen, & Connolly, 2014). Ocular features can include myopia, ectopia lentis, flat cornea, and hypoplastic iris or ciliary muscle causing miosis (Dean, 2007). Detached retina, early glaucoma, and early cataracts are also seen (The Marfan Foundation, 2014a). The integumentary exam in a Marfan patient may reveal stretch marks unexplained by pregnancy, weight loss, or weight gain (The Marfan Foundation, 2014a). Respiratory assessment can consist of a spontaneous pneumothorax, emphysema, asthma, and/or sleep apnea (The Marfan Foundation, 2014a). Cardiac assessment can include an enlarged or bulging aorta, aortic aneurysm, aortic dissection, mitral valve prolapse, or pectus carinatum or excavatum (The Marfan Foundation, 2014a). Dilatation of the pulmonary artery and/or a calcified mitral annulus is also seen as a feature (Dean, 2007). The cardiac features are not as overt as the other features mentioned herein and therefore require expertise in understanding the syndrome for early detection (The Marfan Foundation, 2014b).

DIAGNOSTICS

Because of the multisystem involvement of Marfan syndrome, diagnosing a patient who is suspect of Marfan syndrome requires a diligent practitioner to ensure regular follow-up and continued care to decrease mortality and morbidity. The mean age of diagnosis is 7.3 ± 10 years; however, 10% of people are not diagnosed after the age of 28 years (Sponseller et al., 2010). Because of the lack of specific laboratory tests to diagnose Marfan syndrome, systematic surveillance of body systems ensures early diagnosis. There are four main factors in the diagnosis of Marfan syndrome: the *FBN1* gene mutation, aortic root dilation Z score, ectopia lentis, and a systemic score (Devereux et al., 2012). Imaging is a vital aspect in Marfan syndrome diagnosis and includes transthoracic echocardiogram (TTE),

MRI, CT, and x-rays, which provides valuable information and aids in diagnosing cardiac, orthopedic, and connective tissue abnormalities. However, TTE is the primary imaging tool used to diagnose Marfan syndrome, as TTE values are used in the calculation of aortic dilatation Z-score is essential in gauging aortic involvement to determine risk of Type A aortic dissection (Radke & Baumgartner, 2014). Appropriate testing and collaboration between health care professionals to detect possible Marfan syndrome and make proper referrals is essential in diagnosing Marfan syndrome as early as possible.

Systemic Score

Systemic scoring system was created to evaluate selective systemic features dependent on the presence of clinical features discussed and is a diagnostic tool in Marfan syndrome. Table 1 outlines a checklist with a possibility of 20 points; however, a score greater than seven points is indicative of systemic involvement and a positive finding

for Marfan syndrome (Radke & Baumgartner, 2014).

Ghent Nosology

A guide to diagnosing Marfan syndrome is the Ghent nosology revised in 2010, which outlines seven rules for diagnosis (detailed in Box 1). Using the revised Ghent nosology, the two factors that carry the most weight are the aortic root dilatation Z-score and ectopia lentis (Radke & Baumgartner, 2014). If one of these characteristics is missing, *FBN1* gene mutation is required for diagnosis (Loeys et al., 2010). Ectopia lentis typically develops before the age of 30 years and results in symmetric bilateral lens subluxation, resulting in dislocation and myopia in a supertemporal direction visible upon ophthalmic examination (Lally & Monsonego, 2014). The aortic root dilatation Z-score is a calculated score (detailed in Box 2) based on standard deviations in relation to the actual measurement of the sinuses of Valsalva on echocardiogram and

Table 1. Calculating systemic score

Feature	Value
Wrist <i>and</i> thumb sign	3
Wrist <i>or</i> thumb sign	1
Pectus carinatum deformity	2
Pectus excavatum or chest asymmetry	1
Hindfoot deformity	2
Plain flat foot	1
Spontaneous pneumothorax	2
Dural ectasia	2
Protrusio acetabuli	2
Scoliosis or thoracolumbar kyphosis	1
Reduced elbow extension	1
Three of five facial features—dolichocephaly, enophthalmos, down-slanting palpebral fissures, malar hypoplasia, and retrognathia	1
Skin striae	1
Severe myopia	1
Mitral valve prolapse	1
Reduced upper segment/lower segment and increased arm span/height— $\text{span/height} > 1.05$	1
Score greater than seven is considered a positive systemic score	

Note. Modified from The Marfan Foundation, 2014a.

Box 1. Criteria for diagnosing Marfan syndrome using the revised Ghent nosology

In the absence of family history:

- Aortic root dilatation Z score ≥ 2 and ectopia lentis
- Aortic root dilatation Z score ≥ 2 and *FBN1* present
- Aortic root dilatation Z score ≥ 2 and systemic score ≥ 7 points
- Ectopia lentis and *FBN1* present with known aortic root dilatation

In the presence of family history:

- Ectopia lentis and family history of Marfan syndrome
- A systemic score ≥ 7 points and family history of Marfan syndrome
- Aortic root dilatation Z score ≥ 2 above 20 years, ≥ 3 below 20 years and family history of Marfan syndrome

(Modified from Loeys et al., 2010.)

Box 2. Calculating aortic root dilatation Z score

Z -score normalized for BSA

$$\begin{aligned} \text{Mean predicted AR (cm) for BSA} \\ = 2.423 + (\text{age} \times 0.009) + (\text{BSA} \times 0.461) \\ - (\text{sex} \times 0.267) \end{aligned}$$

$$Z = (\text{measured diameter} - \text{predicted AR}) / \text{SD with an SD of } 0.261 \text{ cm}$$

Z -score normalized for height

$$\begin{aligned} \text{Mean predicted AR (cm) for length} \\ = 1.519 + (\text{age} \times 0.010) + (\text{height (cm)} \\ \times 0.010) - (\text{sex} \times 0.247) \end{aligned}$$

$$Z = (\text{measured diameter} - \text{predicted AR}) / \text{SD with an SD of } 0.215 \text{ cm}$$

Sex: male = 1, female = 2

$$\begin{aligned} \text{BSA (m}^2\text{)} &= (0.007184 \times \text{height in cm})^{0.725} \\ &\times (\text{weight in kg})^{0.425} \end{aligned}$$

(Modified from Devereux et al., 2012.)

the predicted aortic root diameter in relation to body surface area (BSA), age, and sex, the higher the Z -score the higher the likelihood of aortic involvement associated with Marfan syndrome (Devereux et al., 2012).

TREATMENT AND MANAGEMENT

Cardiovascular complications are the cause of an increased mortality and morbidity rate among individuals with Marfan syndrome and can be slowed with early detection and intervention. These cardiovascular complications are due to the rapid increase in aortic size, leading to aortic root dilatation and dissection (Brooke et al., 2008). Genetically, the involvement of the encoding fibrillin-1 (*FBN1*) also leads to the gradual enlargement and dissection of the aortic root (Brooke et al., 2008). Treatment and early detection of cardiovascular complications require consistent monitoring with TTE to detect changes in aortic size. Frequency of TTE is dependent on the patient's health status and discretion of the primary cardiologist.

Prophylactic treatment with angiotensin II-receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and β -blockers has been found to decrease the size of the aortic root and progression of *FBN1* growth (Brooke et al., 2008). The deficiency of fibrillin-1 in the extracellular matrix leads to the excessive signaling by TGF- β , which contributes to the gradual enlargement of the aortic root (Brooke et al., 2008). Losartan, an angiotensin receptor blocker (ARB), was shown to inhibit TGF- β signaling and aortic root growth, decreasing aortic root Z -score and risk of both aneurysm and dissection (Brooke et al., 2008). β -Blocker treatment remains controversial, as some studies show they slow aortic root growth, whereas others suggest that they have no effect or worsen stiffening indexes in greater than or equal to 35% of patients with Marfan syndrome (Milewicz, Dietz, & Miller, 2005). Although ACE inhibitors and ARBs work directly on decreasing aortic growth, β -blockers help indirectly by reducing aortic root pressures and both inotropic and chronotropic activities (Milewicz et al., 2005).

The most effective prophylaxis for aortic root aneurysm is surgical intervention, which has been proven to decrease mortality and morbidity in individuals with Marfan syndrome (Milewicz et al., 2005).

Candidates who warrant prophylactic surgical repair such as aortic valve surgery and aortic root replacement are women with aortic diameters greater than 40 mm who wish to conceive, individuals with aortic diameters greater than 50 mm, and progressive dilatation of greater than 5 mm per year (Schoenhoff et al., 2013). Surgery is recommended in individuals with the presence of moderate to severe aortic regurgitation and those with a family history of premature aortic dissection (Milewicz et al., 2005). The use of mechanical aortic prosthetic valves places patients at risk of hemorrhage, thromboembolism, and endocarditis (David, Armstrong, Maganti, Colman, & Bradley, 2009). Although aortic valve-sparing surgeries do not rely on anticoagulation, they pose less risk for hemorrhage (David et al., 2009).

Although cardiovascular implications make up for more than half of the complications of Marfan syndrome, the musculoskeletal system, ocular, and respiratory systems must be managed to increase patients' quality of life. Scoliosis can persist into adult life, especially if the angle of curvature is more than 40°. This problem can lead to dural ectasia, causing severe chronic back pain and requiring pain medications (Dean, 2007). Patients with Marfan syndrome often encounter structural rib cage abnormalities, such as pectus excavatum or pectus carinatum (Neuville, Jondeau, Crestani, & Taille, 2014). The Nuss procedure, is a surgical intervention that manipulates the sternum using a stainless steel bar, can be considered for management of pectus excavatum in severe cardiovascular or psychological symptoms (Neuville et al., 2014).

Ocular manifestations associated with Marfan syndrome can lead to blindness when not detected and managed early (Pyeritz, 2008). Regular ophthalmology evaluation is imperative to detect ocular changes and should begin in childhood (Pyeritz, 2008). Individuals with ectopia lentis, which occurs in greater than 60% of Marfan individuals, are mainly managed with miotic drugs to keep the pupils constricted (Pyeritz, 2008). Ectopic lentis places patients at increased risk for retinal detach-

ment, the most severe ocular complication (Nahum & Spierer, 2008). Scleral buckling is recommended as the first surgical procedure to decrease incidence of retinal detachment (Nahum & Spierer, 2008). Minor interventions include prescribing glasses and contact lenses for myopic patients to ensure visual acuity (Pyeritz, 2008).

EMERGENCY DEPARTMENT RECOGNITION AND MANAGEMENT

Nurses and advanced practice providers should be able to recognize the physical features of Marfan syndrome and should remain current on established guidelines for clinical management and diagnostic evaluation of the disease (Yip & Sawatzky, 2014). Classically, an individual who is tall and thin, with disproportionately long upper extremity attributes, complaining of chest pain and/or shortness of breath should be evaluated immediately (Swenty, 2015). The astute clinician realizes that these findings may represent aortic dissection, pneumothorax, or aortic valve collagen defects, characteristic of the syndrome. Once identified, the emergent management includes aggressive blood pressure control and heart rate reduction. Ideally, β -blockers would be used to reduce aortic root pressure and dilation, while reducing the β -related heart rate increases (Yip & Sawatzky, 2014). The goals of medical management include: (1) resting heart rate less than 70 beats per minute; (2) exercise-induced heart rate of less than 100; (3) systolic blood pressure less than 120 mm Hg without aortic dissection; and (4) systolic blood pressure less than 100 mm Hg with aortic disease (Yip & Sawatzky, 2014).

Since chest pain is often the cardinal emergent complaint of patients presenting to the emergency department with Marfan syndrome. Early recognition and evaluation of Marfan syndrome is dependent on prompt identification. This identification includes a good medical history, family history, and screen test maneuvers, including the Ghent criteria, of those perceived to be at risk. Given the underlying suspicion of Marfan syndrome,

emergent testing includes an electrocardiogram, chest x-ray, echocardiogram, and chest and abdomen CT. These diagnostic tests are useful in identifying a pneumothorax, cardiac defect, and the extent of thoracic and abdominal aneurysmal dissection, and aid in determining the need for lifesaving emergent surgery (von Kodolitsch et al., 2016). Even with surgical correction, patients with Marfan syndrome may still be at risk for subsequent dilation and dissection and may require additional aortic surgeries (Yip & Sawatzky, 2014). Advanced practice providers should be prepared to make appropriate and necessary referrals, such as to ophthalmologists, geneticists, and cardiologists (Yip & Sawatzky, 2014).

It is imperative for clinicians to know the signs and symptoms of Marfan syndrome to prevent life-threatening conditions with early diagnosis and prompt emergent referrals. Although this article focuses on the serious cardiovascular complications of aortic disease, other connective tissue systems are affected and require integration of multiple specialties. Timely and prompt disease diagnosis and management lead to better outcomes and save patients' lives.

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