Cardiac Complications in Marfan Syndrome: A Review

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Abstract

Marfan syndrome (MFS) is a rare inherited disorder of the connective tissue with an autosomal dominant mode of inheritance which happens as a result of a mutation in the fibrillin-1 (FBN1) gene located on chromosome 15q21.1. This mutation results in the defective formation of microfibrils and increased levels of active transforming growth factor beta (TGF beta), leading to defective connective tissue synthesis. These changes affect various parts of the body but most notably affected are the heart, eyes, and the musculoskeletal system. The standard presenting features of a person suffering from MFS are tall stature with a large arm span, kyphosis, congenital dislocation of the lens (ectopia lentis) and cardiovascular manifestations. The 2010 modified Ghent criteria are used to diagnose MFS on the basis of parameters such as cardiovascular, eye, and musculoskeletal disorders. The cardiovascular manifestations in a patient with MFS are the leading causes of mortality. The most common and dreaded complication is an aortic aneurysm and subsequent dissection. Cardiomyopathy and arrhythmia are also potential killers in such patients. This article aims to look at the various cardiac complications mentioned above and gain an understanding of their pathogenesis, incidence, and outcome. It also includes a brief overview of the rare complication post-Bentall graft infection, and its cause, diagnosis, and management. Various articles by several different authors from around the world were searched for information regarding the pathogenesis, incidence, and outcomes of these patients and are referenced below.

Introduction And Background

Introduction

Marfan syndrome (MFS) is one of the most common autosomal dominant disorders of the connective tissue, with a prevalence ranging from 1.5 to 17.2 per 100000 individuals [1]. There is no male or female sex predilection of the disease, thus seen with equal incidence in both males and females [2]. According to many pieces of research carried out independently across the globe by various researchers, it has been found that the most common etiological factor for the causation of the disease is a gene called fibrillin-1 (FBN1) gene [3]. It is situated on chromosome 15q21.1 and encodes a glycoprotein FBN1, the major component of the microfibrils situated in extracellular matrix [4]. As a result of the mutation, there are many manifestations in the eyes, cardiovascular system, and skeletal system, which are typical in a case of MFS. The clinical picture of the patient suffering from the disease is very typical, with the patient being very tall as a result of disproportionate growth of upper limbs and lower limbs, and the wingspan is more than 1.05 times the height of the person with elongated fingers [4]. The thoracolumbar vertebra also shows scoliosis, a sideward curvature of the spine in more than 60% of the patients diagnosed with this condition [5]. In ocular manifestations, this disease is characterised by ectopia lentis, which is congenital dislocation of the lens that is bilateral [6]. Cardiac manifestations also characterise the condition, the most characteristic of which is the dilation of the aortic root and proximal ascending aorta, which inevitably leads to aortic aneurysm and dissection in the early years of life that is under 40 years of age [7]. Late manifestations in the case of MFS may be aortic valve incompetence leading to aortic regurgitation [8]. The most common cause of death in patients with MFS is the result of aortic dissection with a case fatality rate of 1-3%, which happens in the early years of life [9]. The diagnostic criteria most widely accepted for MFS is called the revised Ghent nosology, which has major and minor criteria made after international expert opinion for accurately recognising the congenital condition to improve management and outcome of the patient [10].

Background

Genetic Basis

The main genetic defect associated with MFS is the FBN1 mutation found on chromosome 15q21.1. It is a large glycoprotein molecule with a molecular weight of 350 kDa, which is synthesised and released by fibroblasts and embedded into the extracellular matrix in the form of insoluble microfibrils [11,12]. These microfibrils serve as a foundation where elastin is deposited and are important for building a proper elastic framework for providing elasticity to dynamic connective tissues [13]. The structure of these fibrils is
Recent research has also shown the adverse effects of Heart Failure diastolic volume and end-systolic volume, which may not be compensated adequately at an increased risk of developing chronic heart failure, which occurs as a result of an increase in end-systolic pressure of patients out of a total of 227 patients [27].

Gene mutation, is observed in up to one-third of adult patients [27]. For instance, aortic regurgitation in the mitral valve was reported in up to 12% of the diagnosed patients by the age of 30 years [25]. Another commonly observed abnormality seen in patients with MFS is valvular regurgitations, namely aortic regurgitation. According to a study by Rybieszynski et al., more than 50% of the patients with MFS report having regurgitation of the mitral valve. Out of those, severe aortic regurgitation in the mitral valve was reported in up to 12% of the diagnosed patients by the age of 30 years [27]. Aortic valve regurgitation, which can be linked to the aortic valve annulus dilation as a result of FBN1 gene mutation, is observed in up to one-third of adult patients [28]. This was shown in a study conducted by Porciani et al., in which mitral valve prolapse was seen in 78.9% of patients and mitral insufficiency in 72.7% of patients out of a total of 227 patients [28].

As a result of chronic valvular insufficiency, these patients are at an increased risk of developing chronic heart failure, which occurs as a result of an increase in end-diastolic volume and end-systolic volume, which may not be compensated adequately [1].

Review

Complications

Aortic Aneurysm and Dissection

The most commonly encountered and the most characteristic feature of a patient suffering from MFS, which is also a major diagnostic criterion along with lens subluxation in the 2010 revised Ghent nosology, is the increase in the diameter of the aortic root. This dilation of the aortic root, which can ultimately lead to dreaded complications like aortic dissection and aneurysm, is the single most important and frequent reason of mortality in a patient with MFS [23]. The condition’s prevalence is shown to be more in adults than in children and has been suggested in a study by Roman et al. according to which the prevalence of aortic root dilation is marginally higher in adults in comparison to children (approximately 90% vs 80%) [24]. The same was also shown by another study by Erkula et al., which showed the prevalence of aortic root dilation in adults and children to be 81% vs 76% [25]. In terms of sex predilection for the development of an aortic aneurysm, it is shown in many studies that males are generally more predisposed to the development of aortic aneurysm than females [24,26]. Similar results were observed for aortic dissection, which was more common in males than females. The cause for the aortic abnormalities can be attributed to the defective microfibrils addressed above as a result of FBN1 mutation and TGF beta overactivity. These lead to defective aortic wall formation, which can cause aneurysm and dissection due to intraluminal pressure and hemodynamic stresses.

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Heart Failure

Recent research has also shown the adverse effects of FBN1 mutation on the contractility of the heart.
muscles. A study conducted by Yetman et al. among 70 patients with MFS with documented cardiac manifestations showed that 34 patients (68%) had a dilated left ventricle and eight patients (11%) had reduced ejection fraction [29]. This was also shown by De Backer et al. in their study, which showed that patients with MFS undergoing MRI revealed a reduction in the ejection fraction as well as in peak systolic velocities and an increase in the end-systolic volume [30].

Though many studies were done on the effect of MFS on left ventricles, not many studies were done regarding the effects on the efficiency of the right heart to pump blood. It changed when a study done by Kiotsekoglou et al. suggested, based on Doppler and conventional echocardiography, that in comparison to controls, MFS patients showed defective right ventricular systolic function, which was expressed as a reduced dp/dt ratio [31]. This was later confirmed by a study done by Alpendurada et al. It suggested that the ejection fraction of the right ventricle was reduced by 10.5%, with an increase in end-diastolic volumes of the right ventricle by 11.8%. Also, end-systolic volume was increased in 13.2% out of a total 68 patients with MFS [32].

Various tests were conducted on lab-bred mice regarding the role of FBN1 gene mutation on MFS-related cardiomyopathy to gain a greater insight into the pathophysiology of MFS. The tests revealed that Fbn1 (C1039G+) mice showed left ventricular contraction dysfunction. Subsequent observations of the heart muscle also revealed upregulation of the TGF beta-related molecular pathway, which was consistently associated with microfibril abnormalities in the mice [33]. Another study conducted by cook et al. suggested that Fbn1mgR/mgR mice synthesised around 20% of the usual amount of fibrillin-1. Such mice ultimately died from ruptured aortic aneurysms during the first year of life. Echo findings also showed significant aneurysms of the aortic root along with proximal ascending aorta and severe regurgitation in mitral and aortic valves [34]. This finding very much correlates to the findings seen in the patients suffering from MFS. This implicates the role of the FBN1 gene in the pathogenesis of cardiac complications.

Thus it can be said that microfibrils play a crucial role in the myocardium. They do so by maintaining the adequate compensated response of the myocardium to various stresses such as volume and pressure overload. In cases where microfibrils are defective, this compensation is lost, and thus, there can be manifestations leading to a reduction of ejection fraction by the heart [3]. The reduced ejection fraction of the heart can lead to an increase in the end-systolic volume and, subsequently, an increase in end-diastolic volume, which can precipitate heart failure, which is observed in patients with MFS The same is also shown in Figure 1.

Abnormal genetic manifestation

- Underlying FBN-1 gene mutation
- Reduced microfibrils and altered TGF beta
- Impaired myocardial contractility and altered valvular anatomy

Manifesting cardiac abnormality

- Altered valvular anatomy
- Manifestations like valvular insufficiency and increased ventricular afterload
- Congestive cardiac failure

FIGURE 1: Flowchart showing genetic factor and its role in the pathophysiology of heart failure

FBN-1 = fibrillin-1; TGF beta = transforming growth factor beta

Image credit: Author Jayant Singh

Arrhythmia

Arrhythmia in the case of MFS is less likely to be seen in comparison to aortic root abnormality and cardiomyopathy, although it has been shown that people with FBN1 gene mutation have a higher prevalence of ventricular arrhythmia by around 48% in comparison to normal people. This was attributed to mutations in exons 24-32 of the FBN1 gene [35]. In a study by Muiño-Mosquera et al., out of total 86 patients suffering from MFS, 20 patients had non-sustained ventricular tachycardia (NSVT). Out of those, 12 patients were...
documented as having previous valvular surgery or valvular dysfunction [36]. It is also shown in many studies that patients with valvular abnormalities and insufficiencies are more at risk for developing arrhythmias [29]. Factor N-terminal pro-b-type natriuretic peptide (NTproBNP) has been implicated, independent of valvular pathologies [1]. It has also been implicated as an independent risk factor in a study by Hoffmann et al., which suggested that values more than 214.3 pg/ml of NTproBNP are associated with sustained ventricular tachycardia and sudden cardiac death [57]. Therefore it can be hypothesised that the presence of arrhythmia in a patient with MFS is mostly not a primary pathology. It is rather a secondary manifestation of cardiomyopathy or heart failure resulting from valvular abnormalities. Table 1 illustrates the results of three studies done by separate authors and their findings in regard to arrhythmia seen in patients with MFS.

| Author          | Study type           | Number of patients | Mode                     | Findings                                      |
|-----------------|----------------------|--------------------|--------------------------|-----------------------------------------------|
| Chen et al. [38]| Follow-up for five years | 24 patients, all children | Resting ECG              | ventricular arrhythmias were observed         |
| Mah et al. [39] | Cross-sectional      | 274 patients, adults and children | 2D echo and Ambulatory ECG | 7% had ventricular arrhythmia                 |
| Yetman et al. [29] | Follow-up for six years | 70 patients, adults and children | 2D echo, Resting E.C.G., and Ambulatory ECG | 21% had ventricular arrhythmia, 6% had non-sustained ventricular tachycardia |

**TABLE 1: Table showing three studies and their results regarding the prevalence of arrhythmias in patients with Marfan syndrome (MFS)**

ECG = electrocardiography; 2D echo = two-dimensional echocardiography

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**Mitral Valve Prolapse**

Mitral valve prolapse is another commonly associated condition seen in patients with MFS. The normal annular height to commissural width ratio (AHCWR) is shown to be around a mean value of 24%. An increase in value indicates more saddle shape and lesser value indicates a planar shape [40]. The normal orientation of the annulus is saddle-shaped as it confers mechanical advantage by adding curvature [41]. A study regarding the three-dimensional structure of the mitral valve and annulus morphology in cases of MFS by Jolley et al. suggested that the AHCWR was reduced in patients with MFS, which was shown to be around a mean value of 20% thus giving it a planar configuration [42]. It has also been shown that the mitral valve leaflets undergo myxomatous thickening and elongation in response to FBN1 gene mutation [43]. A randomized control trial by Lacro and colleagues suggests that the prevalence of mitral valve prolapse and regurgitation is more in females compared to males, being 45% vs 33% in case of prolapse and 25% vs 13% in case of regurgitation [44]. However, another study by Detaint et al. suggested an equal prevalence of prolapse and regurgitation in both genders [26]. It was also shown that the incidence of these complications increases as age increases [26]. The mechanism for the prolapse and subsequent regurgitation has also been attributed to increased TGF beta activity similar to that seen in aortic root dilation [45].

**Post-Bentall Graft Infection**

This is a rare yet serious complication in patients undergoing Bentall graft operation, which has been discussed below. This condition arises due to the prosthetic graft getting infected by gram-positive cocci [46]. The diagnosis is done by a combination of clinical features, radiological findings, and blood reports. It is a late-onset condition in which the patient presents with features like prolonged fatigue and fever. Transthoracic echo is suggested in such cases to assess the anatomy of the ventricles and the aortic root which reveals dilatation of the left atrium and ventricle [47]. Blood reports show elevated leukocytosis and raised C reactive protein (CRP) levels [47].

**Management**

As mentioned above, the most common and fatal cardiac manifestation in a case of MFS is aortic root dilation. Therefore, medical management in these cases includes four main drugs, namely calcium channel blockers, whose action is relaxing the smooth muscles by blocking the calcium channels; angiotensin-converting enzyme inhibitors, which act by inhibiting angiotensin 2 production; angiotensin receptor blockers, which act by inhibiting angiotensin 2 type 1 receptors and thus prevent activation of the renin-angiotensin-aldosterone system (RAAS) to promote diuresis; and beta-blockers, which cause myocardial relaxation by blocking beta-1 receptors. These drugs are believed to delay and prevent aortic root dilation [48]. The most commonly used and accepted drug regimen is a combination of beta-blockers supplemented with angiotensin receptor blockers (ARBs) [49]. In a study in 1970 on a standard model of an aorta...
constructed with Tygon tubing (Saint-Gobain Corporation, Courbevoie, France) and dog aorta, it was suggested that beta-blockers reduced the pressure impulse (dp/dt), which led to limitation of aortic dissection propagation and so is used as a basis of use in humans where it reduces the impact of hemodynamic forces on the aorta [30]. In the case of the ARB, it was shown that RAAS system activation leading to the release of angiotensin 2 led to an increase in TGF beta. This caused exacerbation of aortic aneurysm and dissection and thus formed the basis for the use of ARB [49].

Regarding surgical options, the most effective procedure is aortic root replacement. It is of two types, namely total root replacement (TRR) and valve-sparing root replacement (VSRR) [23]. TRR was introduced by Bentall and De Bono and involves the replacement of the whole of the aortic root with a prosthetic graft along with mechanical valves as a replacement for the organic valves of the aorta [23]. In the case of post-surgical graft infection, surgical removal of the infected graft is the preferred choice of treatment [47]. However, in patients not fit for surgery, prolonged antibiotic therapy (>5 months) is advised [47]. VSRR, on the other hand, as the name suggests, is a procedure which spares the native valves in a patient. It is mostly preferred in young patients as TRR puts them on lifelong anticoagulation. This can put them at risk for haemorrhage and thromboembolic complications [23]. TRR, on the other hand, has the advantage that the procedure can be performed irrespective of aorta dimensions or the degree of aortic regurgitiation [23].

Conclusions

MFS, as mentioned above, is an extremely rare disease but with a very characteristic presentation like tall stature with long limbs and similarly long digits. This enables the physicians to make a clinical diagnosis on the basis of clinical signs such as thumbs extending far beyond the edge of their hands when they make a fist. It can cause a plethora of cardiac complications of which the most fatal and commonly encountered is resultant heart failure. As a result of heart failure, ventricular arrhythmias can also arise. All these factors lead to mortality and morbidity in the patients. Thus such patients must be identified as soon as possible based on clinical features, and 2010 modified Ghent nosology and intervention, which may be medical or surgical, should be initiated. In the initiation of intervention, whether medical or surgical, factors like age and comorbidities should be kept in mind and treated accordingly.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors declare that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Demolder A, von Kodolitsch Y, Muiño-Mosquera L, De Backer J: Myocardial function, heart failure and arrhythmia in marfan syndrome: a systematic literature review. Diagnostics (Basel). 2020, 10:751. 10.3390/diagnostics10070751
2. von Kodolitsch Y, Robinson PN: Marfan syndrome: an update of genetics, medical and surgical management. Heart. 2007, 93:755-60. 10.1136/hrt.2006.098798
3. Robinson PN, Arteaga-Solis E, Baldock C, et al.: The molecular genetics of Marfan syndrome and related disorders. J Med Genet. 2006, 43:769-87. 10.1136/jmg.2005.039669
4. Coelho SG, Almeida AG: Marfan syndrome revisited: from genetics to the clinic. J Hum Genet. 2020, 55:215-26. 10.1016/j.jher.2019.09.008
5. Dean JC: Marfan syndrome: clinical diagnosis and management. Eur J Hum Genet. 2007, 15:724-33. 10.1038/sj.ejhg.5201851
6. Laval J: Bilateral congenital ectopia lentis with arachnodactyly (Marfan’s syndrome). Arch Ophthalmol. 1958, 20:571-4. 10.1001/archoph.1958.00850210027003
7. Ammash NM, Sundt TM, Connolly HM: Marfan syndrome—diagnosis and management. Curr Probl Cardiol. 2008, 33:5-39. 10.1016/j.cpcardiol.2007.10.001
8. El-Masry AA, Dwedar I, Abdel-Halim HA, Hazem R: Marfan syndrome. Egypt J Chest Dis Tuberc. 2013, 62:197-9. 10.1016/j.ejcht.2013.01.008
9. Krause KJ: Marfan syndrome: literature review of mortality studies. J Innsbr Med. 2000, 32:79-88.
10. Loeyts BL, Dietz HC, Braverman AC, et al.: The revised Ghent nosology for the Marfan syndrome. J Med Genet. 2010, 47:476-85. 10.1136/jmg.2009.072785
11. Dietz HC, Loeyts B, Carta L, Ramirez F: Recent progress towards a molecular understanding of Marfan syndrome. Am J Med Genet C Semin Med Genet. 2005, 139C:4-9. 10.1002/ajmg.c.30068
12. Kiely CM, Sherratt MJ, Marson A, Baldock C: Fibrillin microfibrils. Adv Protein Chem. 2005, 70:405-36. 10.1016/S0065-3233(05)70012-7
13. Kiely CM, Baldock C, Lee D, Rock MJ, Ashworth I, Shuttleworth CA: Fibrillin: from microfibril assembly to biomechanical function. Philos Trans R Soc Lond B Biol Sci. 2002, 357:207-17. 10.1098/rstb.2001.0129
14. Zeiger SM, Sloan B, Jones JA: Pathophysiology and pathogenesis of Marfan syndrome. Adv Exp Med Biol.
Stuart AG, Williams A: Batta A, Panda P, Singh H, Sharma YP: review of the literature 165:828-835.e3.
Lacro RV, Guey LT, Dietz HC, et al.: Cardiovasc Transl Res. 2011, 4:741-7.
Jolley MA, Hammer PE, Ghelani SJ, et al.: leaflet stress Salgo IS, Gorman JH 3rd, Gorman RC, et al.: saddle shape Mah DY, Sleeper LA, Crosson JE, et al.: Dis Child. 1985, 139:273-6.
Hoffmann BA, Rybczynski M, Rostock T, et al.: with Marfan syndrome caused by FBN1 mutations Aydin A, Adsay BA, Sheikhzadeh S, et al.: Marfan syndrome Aydin A, Adsay BA, Sheikhzadeh S, et al.: Marfan syndrome Cook JR, Carta L, Bénard L, et al.: 78:256-63.
10.1083/jcb.200608167 Choudhary SK, Goyal A: Aortic root surgery in Marfan syndrome. Indian J Thorac Cardiovasc Surg. 2019, 35:79-86. 10.1007/s12055-018-0761-9
Roman MJ, Devereux RB, Preiss LR, et al.: Associations of age and sex with Marfan phenotype: the national heart, lung, and blood institute GenTAC (genetically triggered thoracic aortic aneurysms and cardiovascular conditions) registry. Circ Cardiovasc Genet. 2017, 10:e001647. 10.1177/1933124716671440
Erkula G, Jones KB, Sporsseller PD, Dietz HC, Pyeritz RE.: Growth and maturation in Marfan syndrome. Am J Med Genet. 2002, 109:100-15. 10.1002/ajmg.05312
Détaint D, Faivre L, Collod-Beroud G, et al.: FBN1 mutation. Eur Heart J. 2010, 31:2225-9. 10.1093/eurheartj/ehq258
Rybyszynski M, Mis TS, Sheikhzadeh S, et al.: Frequency and age-related course of mitral valve dysfunction in the Marfan syndrome. Am J Cardiol. 2010, 106:1048-53. 10.1016/j.amjcard.2010.05.038
Porciani MC, Attanasio M, Lewi Y, et al.: Prevalence of cardiovascular manifestations in Marfan syndrome (Article in Italian). Ital Heart J Suppl. 2004, 5:647-52.
Yetman AT, Borneheimer RA, McCrindle BW: Long-term outcome in patients with Marfan syndrome: is aortic dissection the only cause of sudden death?. J Am Coll Cardiol. 2005, 41:329-32. 10.1016/j.ijcard.2006.08.040
De Backer JF, Devos D, Segers P, et al.: Primary impairment of left ventricular function in Marfan syndrome. Int J Cardiol. 2006, 112:533-8. 10.1016/j.ijcard.2005.10.010
Kiotsekoglou A, Sutherland GR, Moggridge JC, et al.: Impaired right ventricular systolic function demonstrated by reduced atrioventricular plane displacement in adults with Marfan syndrome. Eur J Echocardiogr. 2009, 10:295-302. 10.1093/ejehocard/jen239
Alpendurada F, Wong J, Kiotsekoglou A, et al.: Evidence for Marfan cardiomyopathy. Eur J Heart Fail. 2010, 12:1085-91. 10.1093/eurheartj/hfpq127
Campens L, Bernard M, Truchet B, et al.: Intrinsic cardiomyopathy in Marfan syndrome: results from in-vivo and ex-vivo studies of the Fbn1C1039G/+ model and longitudinal findings in humans. Pediatr Res. 2015, 78:256-63. 10.1016/j.pediatrres.2015.110
Cook JR, Carta L, Bénard L, et al.: Abnormal muscle mechanosignaling triggers cardiomyopathy in mice with Marfan syndrome. J Clin Invest. 2014, 124:1329-39. 10.1172/JCI71059
Aydin A, Adsay BA, Sheikhzadeh S, et al.: Observational cohort study of ventricular arrhythmia in adults with Marfan syndrome caused by FBN1 mutations. PLoS One. 2013, 8:e68121. 10.1371/journal.pone.0081281
Maito-Mosquera L, De Wilde H, Deves D, et al.: Myocardial disease and ventricular arrhythmia in Marfan syndrome: a prospective study. Orphanet J Rare Dis. 2020, 15:300. 10.1186/s13023-020-01581-9
Hoffmann BA, Rybczynski M, Rostock T, et al.: Prospective risk stratification of sudden cardiac death in Marfan’s syndrome. Int J Cardiol. 2015, 167:2539-45. 10.1016/j.ijcard.2012.06.056
Chen S, Fagan LF, Nouri S, Donahoe JL: Ventricular dysrhythmias in children with Marfan’s syndrome. Am J Dis Child. 1985, 139:273-5. 10.1001/archpedi.1985.0210006007024
Mah DY, Sleeper LA, Cronox JE, et al.: Frequency of ventricular arrhythmias and other rhythm abnormalities in children and young adults with Marfan syndrome. Am J Cardiol. 2018, 122:1429-36. 10.1016/j.amjcard.2018.07.006
Gorman JH, Jackson BM, Enomoto Y, Gorman RC: The effect of regional ischemia on mitral valve annular saddle shape. Ann Thorac Surg. 2004, 77:544-8. 10.1016/S0003-4975(03)01354-7
Salgo IS, Gorman JH 3rd, Gorman R, et al.: Effect of annular shape on leaflet curvature in reducing mitral leaflet stress. Circulation. 2002, 106:711-7. 10.1161/01.cir.0000025426.3942e.83
Jolley MA, Hammer PE, Ghelani SJ, et al.: Three-dimensional mitral valve morphology in children and young adults with Marfan syndrome. Am J Soc Echocardiogr. 2018, 31:168-1177.e1. 10.1016/j.echo.2018.06.009
Judge DP, Rofl R, Habashi J, Dietz HC: Mitral valve disease in Marfan syndrome and related disorders. J Cardiovasc Transl Res. 2011, 4:741-7. 10.1007/s12265-011-9314-y
Lacro RV, Gury LT, Dietz HC, et al.: Characteristics of children and young adults with Marfan syndrome and aortic root dilation in a randomized trial comparing atenolol and losartan therapy. Am Heart J. 2013, 165:828-835.e5. 10.1016/j.ahj.2013.02.019
Dietz H: FBN1-related Marfan syndrome. GeneReviews®. Margarite P Adam, David B Everman, Ghayda M Mirzaa, et al. (eds): University of Washington, Seattle, Seattle; 1993.
Machelen P, Greb C, Wirth G, et al.: Graft infection after a Bentall procedure: a case series and systematic review of the literature. Diagn Microbiol Infect Dis. 2017, 88:158-62. 10.1016/j.diagmicrobio.2017.05.002
Batta A, Panda P, Singh H, Sharma YP: Role of PET/CT scan in identifying late-onset graft infection following Bentall procedure. BMJ Case Rep. 2021, 14:e243854. 10.1136/ehr-2021-243854
Stuart AG, Williams A: Marfan’s syndrome and the heart. Arch Dis Child. 2007, 92:351-6.
49. Bin Mahmood SU, Velasquez CA, Zafar MA, et al.: Medical management of aortic disease in Marfan syndrome. Ann Cardiothorac Surg. 2017, 6:654-61. 10.21037/acs.2017.11.09

50. Prokop EK, Palmer RF, Wheat MW Jr: Hydrodynamic forces in dissecting aneurysms. In-vitro studies in a Tygon model and in dog aortas. Circ Res. 1970, 27:121-7. 10.1161/01.res.27.1.121