Cardiovascular manifestations in Marfan syndrome

Cecilia Lazea[1,2], Simona Bucerzan[1,2], Mirela Crisan[2], Camelia Al-Khzouz[1,2], Diana Miclea[1,2], Crina Șufană[2], Gabriel Cismaru[1,3], Paula Grigorescu-Sido[1]

1) Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania

2) Emergency Pediatric Hospital, Cluj-Napoca, Romania

3) Cardiology Rehabilitation Department, Clinical Rehabilitation Hospital, Cluj-Napoca, Romania

Abstract

Marfan syndrome (MFS) is an autosomal dominant inherited disease of the connective tissue with multiorgan involvement (skeleton, cardiovascular, eyes, skin, lungs). Cardiovascular involvement is variable and represents the major cause of morbidity and mortality in Marfan syndrome. We provide a comprehensive description of cardiovascular manifestations in Marfan syndrome, genotype-phenotype correlations and assessment of cardiovascular abnormalities and complications.

Keywords: Marfan syndrome, cardiovascular diseases

Introduction

Marfan syndrome (MFS) is an autosomal dominantly inherited disorder of the connective tissue caused by mutations of the *FBN1* gene which is located on the chromosome 15. *FBN1* gene encodes the fibrillin 1, a glycoprotein which is the major constitutive element of extracellular microfibrils and is essential for the formation of elastic fibres. Mutations in the FBN1 gene have been also linked to other clinical distinct entities: MASS (mitral valve – aorta – skeleton – skin) syndrome, familial ectopia lentis, Weill-Marchesani type 2 syndrome, acromicric dysplasia, geleophysic dysplasia 2, stiff-skin syndrome [1-3].

The clinical presentation of MFS is highly variable by multiorgan involvement affecting the skeleton (disproportionally long limbs, pectus deformities and scoliosis), the eyes (lens luxation), the cardiovascular system (aortic dilatation, mitral valve prolapse), the skin and the lungs. Diagnosis of MFS is based on revised Ghent criteria (Table I). Systemic score includes the following clinical features: wrist and thumb sign, pectus deformity, foot deformity, pneumothorax, ductal ectasia, protrusion acetabuli, increased arm span/height, reduced upper segment/lower segment ratio, scoliosis, kyphosis, reduced elbow extension, facial features, skin stria and mitral valve prolapse [1].

Cardiovascular manifestations

The myriad of cardiovascular involvement which includes distinct manifestations represents the major cause of morbidity and mortality and determines the life expectancy in MFS patients. The most common cardiac abnormalities are dilatation of the aorta and mitral regurgitation. In early childhood cardiac manifestations could be less severe.

Aorta and the aortic valve

Progressive dilatation of the proximal aorta is a very severe manifestation because of risk of aortic dissection or fatal rupture and their prevalence is higher in males and adults (90%) comparing to children. Dilatation of the aortic sinus is most common but distal regions of the aorta and extra-aortic arteries can present aneurysms and dissection, too. Etiopathogenesis of the dilatation of the aorta is based on different embryologic origin of the vascular smooth muscular cells of the aortic root, increased activity of transforming growth factor-β (TGFβ) resulting in inflammation and fibrosis of the aorta and high blood pressure and continuous force from left ventricle torsion to the aortic root [4].

DOI: 10.15386/mpr-2223

Address for correspondence: cecilialazea@umfcluj.ro

Table I. Revised Ghent criteria for diagnosis of MFS [1].

Family history of MFS present	Ao Z score ≥ 2 + EL = MFS
	Ao Z score ≥ 2 + FBN1 mutation = MFS
	Ao Z score ≥ 2 + systemic score > 7 points = MFS
	EL + FBN1 mutation + known Ao = MFS
Family history of MFS absent	EL + family history of MFS = MFS
	Systemic score > 7 points + family history of MFS = MFS

Ao: aortic diameter at the sinuses of Valsalva above indicated Z score or aortic root dissection; EL: ectopia lentis; MFS: Marfan syndrome

Risk factors for aortic dissection in adults are as following: progressive aortic root dilatation and aortic root growth rate >5%/year or >2 mm/year, aortic dilatation >50 mm and family history of aortic dissection [5]. Aortic dilatation and mitral valve prolapse were found in patients with mutations eliminating a cysteine residue [2,3].

Annual imaging of the aorta is recommended, included echocardiography and computed tomography angiography or magnetic resonance angiography to assess the entirety of the aorta. In those patients with accelerated aortic root growth, current guidelines recommend the echocardiography twice a year or more frequent in with rapid growth phase in children [6]. Prophylactic surgery in children is considered in severe aortic insufficiency, aortic size Z score >2-3 or rapid growth in size of the aorta. In adults, prophylactic surgery is recommended for aortic root dilatation >4.5 cm or aortic diameter growth ≥0.5 cm/year [7]. The management of aortic disease in MFS requires treatment with β-blockers, calcium channel blockers, angiotensin type II receptor inhibitors and open surgical reconstruction [6,8]. Endovascular repair techniques may represent a useful adjunct or bridge therapy to open surgical therapy in selected patients [9]. Aortic regurgitation resulting from aortic root dilatation and/or myxomatous valvular degeneration is usually asymptomatic in early stages [4].

Mitral valve

Mitral valve in MFS patients is thickened and elongated secondary to increased activity of TGF-β leading to degeneration of myxomatous tissue [10]. Mitral valve prolapse has a high prevalence (40-77%) which depends on age and is associated with skeletal deformities, ectopia lentis and dural ectasia [11,12]. The anterior leaflet prolapse is most common. Mitral regurgitation has variable severity and heart failure in left ventricle overload may therefore occur.

Calcification of the mitral valve annulus has been reported more frequent than in normal individuals. Mitral regurgitation is associated with premature ventricular beats and non-sustained ventricular tachycardia.

Tricuspid valve

Tricuspid valve degeneration can lead to tricuspid valve thickening, prolapse and regurgitation.

Pulmonary artery

Dilatation of the root of the pulmonary artery have been reported in 54% to 69% of the patients with MFS. Pulmonary artery aneurysm may be also present [13,14].

Cardiomyopathy

Primary intrinsic dysfunction of the myocardium in MFS has been reported and consisted in increased left ventricle dimensions, mildly impaired left ventricle systolic and diastolic function. Advanced imaging techniques as tissue Doppler imaging, strain imaging and cardiac magnetic resonance provided additional evidence for myocardial involvement in MFS [15,16]. Pathogenesis of this cardiomyopathy is based on intrinsic factors as altered TGF-β signaling with secondary reduced amount and quality of the microfibrils and abnormal myocyte mechanosignaling leading to reduced elastic recoil and myocardial stretch and impaired muscle contractility. Regurgitant valvular disease, increased left ventricle afterload act as extrinsic factors leading to increased left ventricle pressure and left ventricle end-diastolic volume and myocardial damage [17].

Heart failure

Heart failure due to volume-overload is present in MFS with severe mitral regurgitation but there are patients who develop ventricular dysfunction independently [17,18].

Aortic branches abnormalities

Aortic branch vessels can be affected in MFS, tortuosity of the carotid, subclavian, vertebral and iliac artery is a quite common feature. Increased tortuosity of the vessels is considered a sign of more aggressive systemic disease.

Extra-aortic aneurysm and dissection is usually a consequence of aortic dissection, but isolated arterial aneurysm which can produce spontaneous dissection have been reported. Spontaneous coronary artery dissection and anomalous coronary artery have been described [18,19].

Arrhythmia

Patients with MFS have an elevated risk for arrhythmia (supraventricular and ventricular arrhythmia). Ventricular arrhythmia (premature ventricular ectopic beats and ventricular tachycardia) is the most frequent and can represent an important cause of death in addition with

aortic dissection and heart failure [18]. Ventricular events were significantly more common in patients with mutations in exons 24-32 of the *FBN1* gene [19]. The pathogenesis of arrhythmia in these cases is myocardial dysfunction which is multifactorial including valve regurgitation with myocardial stretch, increased aortic wall stiffness, prolonged atrio-ventricular conduction and altered depolarization [17,19].

Conclusions

Cardiac morbidity in patients with MFS is high and careful assessment and medical care is required.

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