Cardiovascular Pathology 23 (2014) 261–266

Contents lists available at ScienceDirect

Cardiovascular Pathology

Review Article

Aortopathy in Marfan syndrome: an update

Federico Romaniello [a], Donatella Mazzaglia [a], Antonio Pellegrino [b], Susanna Grego [b], Roberto Fiorito [c], Amedeo Ferlosio [a], Luigi Chiariello [b], Augusto Orlandi [a,*]

[a] Institute of Anatomic Pathology, Dept. of Biomedicine and Prevention, Tor Vergata University of Rome, Via Montpellier, 00133 Rome, Italy
[b] Cardiac Surgery, Dept. of Experimental Medicine and Surgery, Tor Vergata University of Rome, Via Montpellier, 00133 Rome, Italy
[c] General Surgery, Dept. of Biomedicine and Prevention, Tor Vergata University of Rome, Via Montpellier, 00133 Rome, Italy

ARTICLE INFO

Article history:
Received 17 March 2014
Received in revised form 29 April 2014
Accepted 30 April 2014

Keywords:
Marfan syndrome
Thoracic aortic aneurysm
Fibrillin-1
TGF-β
Smooth muscle cells
Matrix metalloproteinases
Erk
Oxidative stress

ABSTRACT

Marfan syndrome (MFS) is an inherited autosomal dominant multisystem disease caused by mutations in the *FBN1* gene encoding fibrillin-1, an extracellular matrix glycoprotein widely distributed in mesenchymal-derived tissues that provide a scaffold for elastin deposition. MFS is characterized by variable clinical manifestations, including skeletal, ocular, and cardiovascular abnormalities; ascending aortic aneurysm with ensuing dissection and rupture is the main life-threatening cardiovascular manifestation of MFS. Histological aspects of MFS aortopathy include a medial degeneration from disarray and fragmentation of elastic fibers and accumulation of basophilic ground substance areas depleted of smooth muscle cells (SMCs). Transmission electron microscopy well evidences the high number of interruptions and the thick appearance of the elastic lamellae and the accumulation of abundant extracellular glycosaminoglycan-rich material, sometimes SMCs showing a prevalent synthetic phenotype. The aberrant signaling of transforming growth factor-β (TGF-β) as the consequence of the altered structure of fibrillin-1 induces activation and the overexpression of Smad-dependent profibrotic signaling pathway and ERK1/2-mediated increased synthesis of matrix metalloproteinases. In addition, MFS is accompanied by an impaired aortic contractile function and aortic endothelial-dependent relaxation, which is caused by an enhancement of the oxidative stress and increased reactive oxygen species during the progression of the disease. Many studies are currently evaluating the contribution of TGF-β-mediated biomolecular pathways to the progression of MFS aortopathy and aneurysm development, in order to discover new targets for pharmacological strategies aimed to counteract aortic dilation.

1. Introduction

Marfan syndrome (MFS) is a connective tissue disorder caused by mutations in *FBN1* gene encoding for the extracellular glycoprotein fibrillin-1. The large amount of mutations results in a wide fenotypic variability even though the cardiovascular pathology is the most life-threatening, in particular, aortic root aneurysm progressively leading to dissection and rupture if surgically untreated. The altered structured of fibrillin-1 leads to MFS aortopathy, microscopically characterized by fragmentation of elastic lamellae and loss of smooth muscle cells (SMCs) replaced by basophilic material. The altered fibrillin-1 induces the aberrant signaling of transforming growth factor-β (TGF-β), the overexpression of Smad-dependent profibrotic signaling, and the extracellular signal-regulated kinase 1/2 (ERK1/2)-mediated increased synthesis of matrix metalloproteinases (MMPs). In addition, MFS is accompanied by an impaired aortic contractile function and endothelial-dependent relaxation from enhanced parietal reactive oxygen species-mediated oxidative stress. The relevant role of TGF-β in determining the progression of the aortic dilatation in MFS has suggested blocking pharmacological strategies in parallel with Losartan to reduce the parietal stress. In this review, we reported an integrated view of MFS, highlighting the biomolecular pathways causing patients' aortopathy.

2. MFS: generalities

MFS was first described in 1896 by the French pediatrician Antoine Bernard-Jean Marfan [1]. MFS is an autosomal dominant, multisystem disease caused by mutations in the *FBN1* gene [2]. The latter is a 230-kb gene encoding the structure of fibrillin-1 protein, an extracellular matrix glycoprotein widely distributed in elastic and nonelastic tissues. Mutations in fibrillin-1 in approximately 75% of the cases are inherited from the affected parents, while in the remaining 25% of cases are de novo mutations. The estimated prevalence of MFS ranges from 0.5 to 1 in 10,000 live newborns and equally affects males and females, with no ethnic or geographical or gender bias [3]. Diagnosis of MFS can be challenging because many of its features are age dependent, whereas others are frequently seen in the general population with a substantial phenotypic variability and, finally, because there is a considerable overlap with other connective tissue disorders.

This work was partially founded by an Italian Ministry of Health grant (2013).
* Corresponding author.
E-mail address: orlandi@uniroma2.it (A. Orlandi).

http://dx.doi.org/10.1016/j.carpath.2014.04.007
1054-8807/

Genetic screening of MFS is not routinely used and the diagnosis is made according to the clinical criteria of the Gent nosology [4]. The latter comprises a set of major and minor manifestations. In particular, the Gent nosology puts more relevance on two of the cardinal features, that is, the aortic root aneurysm and the ectopia lentis. In the absence of any family history, the presence of these two manifestations is sufficient for the diagnosis of MFS. The likelihood of the finding of a fibrillin-1 pathological mutation in a patient with diagnosis of MFS according to the Ghent criteria is above 95% [5]. This high specificity suggests that clinical diagnosis based on the presence of clinical features is quite reliable. Nevertheless, in the absence of either of those cardinal features, the presence of a fibrillin-1 mutation or a combination of systemic manifestations is required. Similarly, genetic screening appears more appropriate in order to discover new cases in MFS families [5]. Many disorders are often clinically difficult to distinguish from MFS. In particular, patients with familial ectopia lentis, mitral valve, aortic, skin and skeletal (MASS) phenotype, and familial aortic aneurysm share with MFS clinical manifestations and, in some cases, fibrillin-1 mutations [6]. Since structural tissue abnormalities in combination with high blood pressure drastically increases the risk of acute aortic medial dissection, new recent insight in the respect of pharmacotherapy of MFS includes the Angiotensin II receptor blocker Losartan, which reduces blood pressure and aortic dilatation and stress [7], sometimes in association with inhibitors of TGF-β signaling (see after). Although there are those promising results for the medical management of MFS patients, currently, only the prophylactic surgical treatment with replacement of the entire aortic root effectively increases life expectancy [8,9].

3. Fibrillin-1

Fibrillin-1 is a 350-kD multidomain glycoprotein encoded by the *FBN1* gene containing 65 exons spanning 235 kb of genomic DNA on chromosome 15q21.1 [10,11]. Fibrillin-1 is thought to form the molecular scaffold for a class of 10–12-nm extracellular microfibrils that are distributed in many elastic and nonelastic tissues [12,13]. Fibrillin-1 also binds integrin receptors of SMCs and is suspected to transmit cell-matrix positioning signals [14]. Fibrillin-1 has a modular structure comprising 47 epidermal growth factor-like domains, seven TGF-β1 binding protein-like domains, one proline-rich region, some hybrid modules and a unique N- and C-terminal domain [15,16]. Epidermal growth factor modules are approximately 45-long residues and characterized by six conserved cysteine residues forming three disulfide bounds [17,18]. All cysteines in fibrillin-1 are evolutionarily conserved, emphasizing their essential function [19]. Fibrillin-1 mutations generally break microfibril formation and weaken the connective tissue, resulting in an abnormal fibrillin-related meshwork with poor elastin filaments alignment and disorganization of lamellar units and a final instability of the aortic wall [20]. Reported *FBN-1* gene mutations are spread throughout the gene and include missense, in-frame deletions due to exon-skipping/splice-site mutations or genomic deletions, frameshift, and nonsense mutations leading to premature termination codons [21–24].

FBN-1 gene mutations result in a constellation of phenotypes. MFS is the clinical manifestation most commonly associated with significant cardiovascular pathologies [25]. Among the latter, ascending aortic aneurysm, mitral valve prolapsed, and bicuspid aortic valve have been documented in patients with *FBN-1* gene mutations [26–28]. Nevertheless, beyond the classical cardiovascular phenotype, *FBN-1* gene mutations have also been identified in a range of conditions including the MASS phenotype, familial ectopia lentis, isolated skeletal features, and Weill–Marchesani syndrome [29–32].

4. MFS: clinical aspects

The patients affected by MFS often show a characteristic habitus of elongation and narrowness of the long bones with tall stature and long slender limbs, decreased skeletal muscle mass, scoliosis, and pectus excavatum or carinatum, arachnodactyly [33]. Clinical manifestations of MFS may be multiple and more evident with age. Ectopia lentis represents the main ocular MFS feature affecting nearly 60% of individuals [34]. Myopia tends to show early onset and rapid progression; retinal detachment and glaucoma can occur. Lumbosacral dural ectasia is present in above 90% of MFS patients [35]. Aortic root aneurysm and ensuing aortic dissection and rupture represent the main leading cause of premature death [36,37]. By age 60 years, more than 95% of MFS patients develop a dilation of ascending aorta, and about 75% are subjected to aortic dissection if prophylactic surgery is not performed; aortic complications may also affect patients under 30 years of age [38]. Several indices are associated with increasing risk in Marfan patients. Among these, the most relevant is the size of the proximal aorta [39]. Aortic diameter >5.0 cm is strongly predictive of elevated risk of aortic dissection and rupture [40]. Surgical preventive intervention at that stage is mandatory. Aortograms may show a dilated aortic root or diffuse aneurysmal dilation of the ascending aorta in severe MFS cases [41]; in addition, the increase in size of the proximal aortic root over the time is quite relevant. A rapid increase in aortic size (>0.5 cm/year) increases the risk of dissection. A family history of early aortic complications is also strongly predictive of decreased event-free survival [8]. MFS patients can die from other cardiovascular complications, in particular, severe mitral regurgitation and arrhythmias [42,43].

Because the most prominent dilatation of the MFS aorta is located proximally, transthoracic echocardiography is normally adequate for routinary visualization and measurement of the aortic root in MFS patients (Fig. 1A) [44,45]. In those cases in which echocardiography may result technically inadequate, cardiac magnetic resonance or computed tomography (Fig. 1B) is also available [46]. In any case, annual echocardiographic monitoring of proximal aortic size and rate of growth is essential in MFS patients.

5. Microscopic and ultrastructural aspects of MFS aortopathy

The normal thoracic aorta consists of three well-defined layers: intima, media, and adventitia. The intima consists of a monolayer of endothelial cells that adhere to the basement membrane, which consists primarily of type IV collagen and laminin [47]. The tunica media occupies nearly 80% of the wall and consists of layers of SMCs alternated with elastic laminae; Types I, III, and IV collagen; glycosaminoglycans, and proteoglycans to constitute functional lamellar units. The latter have both tensile strength and elastic recoil properties, and their composition, thickness, and tension are maintained across different species, although their number decreases in the abdominal aorta [48,49].

The earliest recognition of the tissue abnormalities underlying aortic dilation in MFS is the so-called *medial degeneration*, characterized by fragmentation and disarray of elastic lamina, loss of SMCs, and replacement by basophilic and alcianophilic glycosaminoglycans (GAGs) (Fig. 2). The lacunar appearance of medial degeneration from the extracellular accumulation of GAG-rich basophilic material and the relative paucity of cells led to coin the term by Erdheim of cystic medial necrosis [50] even though the tunica media does not really develops cysts or necrosis. Medial degeneration is incorrectly thought to be pathognomonic of MFS aortopathy, but it is nonspecific and can occur in other aortic diseases, including hypertension-related aortopathy [51]. Increased aortic alcianophilia of the tunica media and diffuse intimal thickening observed in MFS also resemble those observed with aging [52].

Medial degeneration is believed to be caused by mutations in fibrillin-1 that destabilize the protein itself, making it more susceptible to proteolytic degradation [53–55], resulting in fragmentation of microfibrils and elastic lamellae, and increased susceptibility to hemodynamic injury. This hypothesis has been initially used to explain the progressive proximal aorta dilatation [56]. Nevertheless, that hypothesis does not completely explain other mesenchymal tissue changes, such as the bone overgrowth and/or osteopenia, the reduced mass of skeletal muscle and adipose tissues, and the craniofacial abnormalities observed in MFS patients [57].