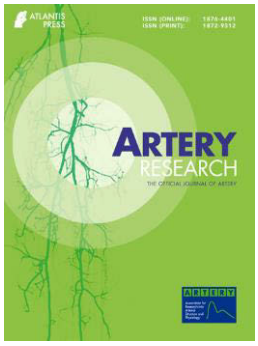

ATLANTIS PRESS

Artery Research

ISSN (Online): 1876-4401 **ISSN (Print): 1872-9312**
Journal Home Page: https://www.atlantis-press.com/journals/artres

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To cite this article: J. De Backer, B. Loeys, A. De Paepe (2009) Marfan and Marfan-like syndromes, Artery Research 3:1, 9–16, DOI: https://doi.org/10.1016/j.artres.2009.01.003

To link to this article: https://doi.org/10.1016/j.artres.2009.01.003

Published online: 14 December 2019

Artery Research (2009) 3, 9–16

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/artres

REVIEW

Marfan and Marfan-like syndromes

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Received 23 October 2008; received in revised form 8 January 2009; accepted 19 January 2009
Available online 3 March 2009

KEYWORDS
Marfan syndrome;
Familial thoracic aortic aneurysm;
genetics;
Marfan-like syndrome

Summary With the help of both clinical and genetic diagnostic tools, the spectrum of inherited disorders affecting the arterial system has extended tremendously over the past decades. Discriminating these different entities is important since prognosis and treatment may differ substantially according to the diagnosis. Here we provide an overview of the current clinical and genetic knowledge on classic Marfan syndrome as well as on Marfan related disorders. Through our increased understanding of the pathophysiological mechanisms underlying aneurysm formation in these monogenetic conditions, new therapeutic strategies have emerged and are now being developed. This may serve as a nice example of translational medicine were detailed knowledge of the complex molecular pathways in rare disorders may help us to improve diagnosis and treatment of more common conditions.

Contents

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doi:10.1016/j.artres.2009.01.003

Since the first description of Marfan syndrome (MFS) more than a century ago, medicine has evolved dramatically. Imaging techniques have been optimized, enabling us nowadays not only to visualize very slight anatomic vascular lesion but also to study functional vascular changes. Both medical and surgical treatment for the cardiovascular lesions associated with MFS has been developed and optimized, leading to a spectacular increase in life expectancy. Last but not least, the recent developments in genetic studies have enabled us to look at the central cause of the problem and will finally give us the opportunity to study the complex pathophysiology leading to aneurysm formation. This will undoubtedly guide our ongoing search for optimal treatment in these patients.

From a cardiovascular point of view, MFS is mainly characterized by aneurysm formation in the proximal ascending aorta, leading to aortic dissection or rupture at a young age when left untreated. This cardiovascular phenotype has served as a major paradigm for the study of aortic aneurysms in general. The identification of the underlying genetic cause of MFS, namely mutations in the fibrillin-1 gene (*FBN1*), has further enhanced our insights into the complex pathophysiology of aneurysm formation.

Based on clinical findings, it has become clear that some patients, although displaying very similar cardiovascular phenotypes do not fit within the diagnosis of MFS. In these instances, the term Marfan-like syndrome has often been applied. With the rapid progression in genetic diagnostic techniques, it is now becoming clear that these entities have a different cause. Our insights into the underlying genetics are steadily growing and the complex disease causing mechanisms are being unravelled bit by bit.

Molecular genetics

Correct understanding of this molecular background is important for the establishment of a correct diagnosis and for guidance of treatment and follow-up in patients with thoracic aortic aneurysms.

Molecular genetics has not only allowed us to improve diagnostic accuracy, but also altered our insights into the pathophysiology of connective tissue disorders. MFS is an autosomal dominant connective tissue disorder caused by mutations in the Fibrillin-1 gene (*FBN1*).[1] Until recently, the underlying pathogenesis of aneurysm formation in MFS was considered to be a consequence of structurally abnormal fibrillin-1 fibers. Conventional wisdom held that microfibrils are essential for elastogenesis and that elastic fiber formation is virtually complete after early postnatal life.[2] It was believed that MFS was essentially a ''structural'' disease, caused by deficient microfibers.

However, recent work using genetically engineered mouse models of MFS has tested and ultimately refuted this hypothesis. Importantly, these models recapitulate most phenotypic alterations in MFS including a specific predisposition for progressive deterioration in aortic wall architecture, aortic root enlargement and aortic dissection leading to premature sudden death.[3–5] Despite an early and severe deficiency of microfibrils, mutant mice show normal elastin content and elastic fiber architecture early in postnatal life. With time, they demonstrate elastic fiber fragmentation and disarray, excess production of matrix elements and matrix-degrading enzymes, and inflammation, all features of the so-called ''cystic medial necrosis'' that has been documented in the human condition. In essence, these data document that fibrillin-1 and microfibrils are not needed for elastic fiber formation, as originally inferred, but rather contribute to elastic fiber homeostasis in postnatal life.[5,6] Inherent to this paradigm is the newly recognized opportunity for productive therapeutic intervention.

Further investigations have led to the recognition that fibrillin-1 fibers play an important functional role in the complex TGF-β pathway. Sakai and colleagues demonstrated that fibrillin was homologous with the family of latent TGF-β binding proteins (LTBPs), which serve to hold TGF-β in an inactive complex in various tissues, including the extracellular matrix. Researchers showed that fibrillin can bind TGF-β and LTBPs.[7–10]

Dietz and colleagues hypothesized that abnormal fibrillin, or reduced levels of fibrillin, in connective tissue might result in an excess of active TGF-β.[11] The current hypothesis is that fibrillin-1 participates in the regulation of TGF-β signalling through direct interaction between the large latent complex and the matrix. Since the large latent complex binds TGF-β, abnormal fibrillin-1 fibers will lead to failed matrix sequestration of the latent TGF-β complex and hence to increased amounts of active TGF-β, which is in turn at the basis of the pleiotropic manifestations in MFS.[11] The involvement of the TGF-β pathway in cardiovascular abnormalities such as mitral valve prolapse and aortic root aneurysm has been confirmed.

In accordance with these observations, very similar findings have been observed for other connective tissue disorders, implying an important role for the TGF-β pathway in the pathogenesis of aneurysm formation.

Cardiovascular lesions in Marfan syndrome

The diagnosis of MFS is based on the identification of major and minor diagnostic criteria in the skeletal, ocular, cardiovascular and central nervous organ systems. Major criteria include a combination of 4 out of 8 skeletal features, lens dislocation, dural ectasia and aortic root dilatation/dissection.[12]

Minor cardiovascular criteria include mitral valve prolapse and pulmonary artery dilatation.

Clinical manifestations in MFS vary widely both within and between families. Severe cardiovascular phenotypes exist with significant AV valve dysfunction and/or rapidly progressive aortic root dilatation, so-called ''neonatal MFS''.[13–15] In the more common, so-called ''classic MFS'', cardiovascular manifestations tend to develop in adolescence, although the absence of manifestations until later in life has also been reported.[16,17]

Dilatation of the ascending aorta

The primary cardiovascular manifestation in MFS is progressive dilatation of the aortic root eventually leading to aortic dissection or rupture. It is estimated that aortic root dilatation is present in >80% of adult MFS patients.[18]

Aortic root dilatation in MFS occurs typically at the sinuses of Valsalva and is defined as an aortic root diameter above the upper limit of the 95% confidence interval of the distribution in a large reference population. Aortic dilatation can be easily detected by plotting observed aortic root diameter versus BSA on previously published nomograms.[19]

The predilection for the ascending aorta to dilate is a result of both structural and local hemodynamic factors. Both the aortic root and the proximal part of the pulmonary artery (which also dilates in MFS, see below) are derived from the neurologic crest, whereas the more distal arterial structures stem from the mesodermis. It has been demonstrated that the elastic fiber content is higher in the ascending aorta than in any other region of the arterial tree.[20] Diseases such as MFS affecting elastic fiber integrity will therefore manifest more easily in this region. Furthermore, it is primarily the ascending portion of the aorta which is subjected to the repetitive stress of left ventricular ejection, eventually resulting in progressive dilatation.[21,22] Since pressures in the aorta are significantly higher than in the pulmonary artery, dilatation will be more pronounced at the aortic root.

In order to define indications for surgical intervention, absolute growth of the aortic root should be reported in addition to the diameter. Annual growth of rates exceeding 1 cm/yr is considered as a risk factor for dissection.

Dissection of the ascending aorta

As a consequence of the progressive dilatation of the ascending aorta, dissection or rupture may occur.

In patients with aortic aneurysms not associated with connective tissue disorders, the degree of aortic dilatation is well correlated with the risk of aortic rupture or dissection.[23] The risk rises substantially when the diameter exceeds 55 mm.

By contrast, in patients with MFS, risk of aortic rupture or dissection and degree of aortic dilatation does not appear to depend solely on the degree of aortic dilatation.[24] Some patients develop aortic dissection at diameters below 55 mm.[25,26] Silverman and colleagues demonstrated that a family history of severe cardiovascular disease in MFS is associated with increased aortic diameter and decreased survival.[27]

Other possible risk factors have been studied such as central pulse pressure[28] and aortic stiffness,[29–32] but none of these have a higher predictive value than the absolute aortic diameter. Aortic stiffness appeared to have a diagnostic value in young patients in one study.[33]

In daily clinical practice, these parameters are not easy to apply since no accurate cut-off values are available.

Mitral valve prolapse (MVP)

In a survey on 166 MFS patients, more than 50% were identified with auscultatory or echocardiographic evidence of MVP.[34] In our own series, we observed MVP with echocardiography in 66% of MFS patients — 35% of whom had classic MVP.[35]

Main pulmonary artery dilatation

Guidelines for the assessment of main pulmonary artery (MPA) dilatation are scarce in the literature. Nollen and colleagues clearly demonstrated increased diameters assessed with Magnetic Resonance Imaging (MRI).[36] Using a cut-off value of 28 mm at the level of the MPA root, they report a prevalence of MPA dilatation of 74%. In our own series with echocardiography, we proposed a cut-off value of 23 mm to define main pulmonary artery dilatation in adult MFS patients.[35]

Complications arising from MPA dilatation are mild. Pulmonary regurgitation is reported in many MFS patients.[37] Pulmonary artery dissection however is very rare.

Dilatation or dissection of the descending aorta

Complications in the descending aorta occur in a minority of MFS patients.[38,39] Marfan syndrome patients presenting with thoraco-abdominal aortic aneurysm/dissection are reported in a few case reports.[40,41] Other reports on the descending aorta in MFS patients are mainly limited to surgical data describing the occurrence of primary or secondary complications in the descending aorta necessitating surgical intervention. Finkbohner and colleagues report that 15% of their patients had a first surgical intervention involving portions of the descending aorta.[38] Nollen and colleagues report on increased growth (defined as >1 mm/yr) in a small subset of patients (6% in the descending thoracic aorta and 7% in the abdominal aorta. They also demonstrated that aortic stiffness is an independent predictor of progressive abdominal aortic dilatation.[42]). Kawamoto and colleagues studied the progression of thoraco-abdominal aortic diameters in MFS patients after surgical repair and defined a subgroup of patients showing progressive dilatation of the distal aorta (>3 mm yr).[43]

Guidelines for the assessment of descending aortic dilatation are lacking in the literature. In our own series of

29 MFS patients studied with MRI, we noted increased diameters at different levels of the descending aorta. However, there was too much overlap with normal controls to define cut-off values. We found no significant correlations with the proximal aortic diameter, although dilatation occurred more frequently in patients with previous aortic root surgery.[35]

With our current knowledge of the existence of Marfan-like conditions, such as Loeys–Dietz syndrome (see below), it is important to note that some Loeys–Dietz syndrome patients may have been included in older reports on MFS – especially patients with widespread vascular involvement should be carefully reconsidered.

Interestingly, abnormal elastic properties of the aorta are not confined to the ascending aorta, but are also detected in the normal sized, more distal parts of the vessel[30] and this as well in patients having previously undergone aortic root surgery as in unoperated MFS patients.[44] Local distensibility of the descending thoracic aorta appeared to be an independent predictor of progressive descending aortic dilatation.[42]

Left ventricular dysfunction

Although not included in the diagnostic criteria for MFS, dilated cardiomyopathy, beyond that explained by aortic or mitral valve regurgitation, seems to occur with higher prevalence in patients with MFS, perhaps implicating a role of the extracellular matrix protein fibrillin-1 in the cardiac ventricles.[18]

Left ventricular (LV) dysfunction in MFS may occur as a consequence of valvular heart disease. However, there is recent evidence suggesting that LV function may be impaired irrespective of the presence of valvular heart disease, as indicated by increased LV dimensions in a subset of patients.[45] In addition it has been demonstrated in a few small studies that left ventricular diastolic function is also impaired in MFS.[46–48]

We performed a detailed study of left ventricular systolic and diastolic function and observed significant impairment in MFS patients using dedicated techniques such as Tissue Doppler Imaging and MRI.[49]

Medical treatment of aortic dilatation in Marfan syndrome

Beta-adrenergic receptor blockade to delay or prevent aortic aneurysm and dissection is commonly used for patients with MFS. The rationale for this treatment strategy is primarily to decrease proximal aortic shear stress, or d*P*/d*T*. Beta-blockers (BBs) are likely beneficial both through negative inotropic and negative chronotropic effects. The majority of published studies has demonstrated benefit of treatment with BBs in MFS, including in children.[50] The only randomized trial assessing the effect of beta-blockade in patients with MFS was published in 1994.[51] Using an open-label protocol, the investigators treated 32 of 70 enrolled patients with propranolol using a dose targeted for a heart rate below 100 beats per minute during exercise or resulting in a 30 percent increase in the systolic time interval (corrected for the heart rate). Patients were analyzed for aortic growth. Fewer patients treated with propranolol reached a primary clinical endpoint of aortic regurgitation, aortic dissection, cardiovascular surgery, congestive heart failure, and death (5 in treatment group, 9 in control group). Furthermore, the normalized rate of aortic dilatation was lower in the propranolol group compared to the control group (0.023 versus 0.084 per year, $p < 0.001$).

Data from trials that have assessed the use of pharmacologic therapy for aortic aneurysm in MFS show that aortic growth is not stopped or reversed, but typically is slowed in response to treatment. The use of BBs does not prevent attainment of other important clinical endpoints including aortic valve dysfunction, surgery, dissection and death in all patients. Although advances in therapy have improved life expectancy, individuals with MFS continue to suffer significant cardiovascular morbidity and mortality.

Recent studies in a FBN1-deficient mouse model of MFS with a susceptibility to aortic dilatation and dissection, similar to that seen in humans with MFS, showed that postnatal treatment with losartan, an angiotensin II receptor blocker (ARB), normalized aortic root growth and aortic architecture, preventing aortic aneurysms and premature death.[52] In the human setting, similar results have been obtained in a small group of severe MFS in children.[53] Large scale trials in more classic forms of MFS are currently recruiting patients.[54]

Marfan-like syndromes

Loeys–Dietz syndrome

Loeys–Dietz syndrome is an autosomal dominant disorder caused by mutations in either of the Transforming Growth Factor Beta Receptor genes (TGFBR1&2). It is clinically characterized by aortic aneurysms and dissections, widespread arterial tortuosity/aneurysms, bifid uvula and hypertelorism (wide spaced eyes).[55] The expression of the disease is variable between and within families.

When compared to MFS, the natural history of LDS patients is significantly worse, as a consequence of cardiovascular complications. The mean age at the first major cardiovascular complication is 27 yr.[5]

Another illustration of the more aggressive course of the arterial disease is the documentation of ascending aortic dissection at root diameters of 40–45 mm in several patients, which is well below the classical surgical limits applied in MFS where dissection of the aortic root commonly occurs at diameters >55 mm.

In addition to the increased disease progression, the lesions are also more widespread in LDS when compared to MFS. Aortic aneurysms and dissections in more distal parts of the aorta are more common in LDS (20% in our series versus estimates of 7–17% in MFS).[38,42] In LDS, aneurysms may also develop outside the aorta in large and middle sized arteries, whereas aneurysm formation in MFS is generally confined to the aorta.

Finally, additional congenital cardiac anomalies including patent ductus arteriosus, bicuspid aortic valve, mitral valve prolapse and atrial septal defect are present with a higher than normal frequency in LDS patients.[56] Williams et al. demonstrated that surgical outcome in LDS patients is good[57]

which is in strong contrast to vascular Ehlers–Danlos Syndrome, known as a ''surgical nightmare'' due to the extreme fragility of the vasculature and skin.[58] Many LDS patients in the study by Williams underwent repeated interventions, usually in different parts of the aorta with good outcome.

Vascular Ehlers–Danlos syndrome (EDS)

Vascular EDS is an autosomal dominant connective tissue disorder caused by mutations in the collagen type 3 gene (COL3A1). It is clinically characterized by joint hypermobility, skin abnormalities (cigarette paper scars, easy bruising, soft velvety skin), fragility of intestinal and genito-urinary organs and vascular fragility leading to dissection or rupture of medium to large muscular arteries.

Typically in vascular EDS, dissections often occur without preceding dilatation/aneurysm formation. In vascular EDS patients, complications in early childhood are rare. The average age at the time of a first complication in the large series reported by Pepin and colleagues was 23.5 years, with rupture of the gastrointestinal tract likely to occur at an earlier age than arterial rupture.[58] About half of the arterial complications in vascular EDS involved the thoracic or abdominal arteries and the rest were divided equally between the head, neck the limbs.[58]

In vascular EDS, the reported incidence of fatal complications during or immediately after vascular surgery is around 45%.[58,59]

In patients with vascular EDS increased circumferential wall stress has been demonstrated at the level of the carotid arteries. It is hypothesized that abnormally low intima-media thickness generates a higher wall stress and may thus increase the risk of arterial dissection and rupture.[60]

Arterial tortuosity syndrome (ATS)

ATS is an autosomal recessive disorder, caused by mutations in a glucose transporter gene (*GLUT10* gene).[61]

In ATS arterial tortuosity is the most prominent clinical feature, along with large artery stenosis. Aneurysm formation of the aorta and large arteries occurs in ATS, although to a lesser extent than in LDS.

ATS patients require imaging studies of the entire vascular tree such as CT or MRI.

Thoracic aortic aneurysms and dissections (TAAD)

Familial TAAD is genetically heterogeneous with 2 loci and 3 genes being identified so far: FAA2 at 5q13–q14, FAA1 at 11q23.3–q24, *TGFBR2, MYH11* and *ACTA2*.

By definition, the entity of TAAD is restricted to those cases presenting with ''isolated'' TAAD – as opposed to the known syndromes such as MFS and LDS. In practice, most reported families also exhibit some additional clinical features.

Pannu and colleagues reported the presence of *TGFBR2* mutations in 4 unrelated families with TAAD.[62] Imaging studies were limited to echocardiographic examination of the ascending aorta. Nevertheless, some patients included in the study did have vascular anomalies outside the aorta (2 carotid artery aneurysms, 3 cerebral aneurysms and 2 abdominal artery/popliteal artery aneurysms) or in the descending aorta (4 patients with a type B dissection) and one patient with enlargement of the pulmonary artery, further raising the suspicion for LDS.

Guo et al. reported on a family with TAAD whether or not in combination with livedo reticularis and iris flocculi, associated to mutations in the smooth muscle alpha-actin (*ACTA2*) gene.[64]

The patients reported by Zhu and colleagues[63] with mutations in the *MYH11* gene, had a clear association with PDA. In their patients there also appears to be a clear association with intracranial dissections and aneurysms whereas manifestations in the distal aorta appear less common. The MYH11 mutations specifically affect the C-terminal coiled-coil region of the smooth muscle myosin heavy chain, a specific contractile protein of smooth muscle cells. All individuals bearing the heterozygous mutations, even asymptomatic, showed marked aortic stiffness, indicated by a lower compliance (66% decrease) and a higher pulse wave velocity (73% increase). A recent study with MRI in patients with MYH11 mutations demonstrated impairment of aortic compliance despite normal aortic size.[65] The authors conclude that heterozygous MYH11 mutations lead to an early and severe decrease in the elasticity of the aortic wall, consistent with the role of the smooth muscle cells in maintaining the aortic properties of the aorta.[66]

Thoracic aortic aneurysms and dissections associated with bicuspid aortic valve

The bicuspid aortic valve (BAV) affects 1–2% of the population and is associated with abnormalities of the aortic wall such as coarctation of the aorta, aortic dissection and aortic aneurysm.[67] Aortic wall abnormalities associated with BAV are characterized by cystic medial necrosis,[68,69] the same process observed in the aorta of patients with Marfan syndrome. Cystic medial necrosis in BAV patients has been demonstrated in the aortic wall of patients with BAV, even without significant aneurysm formation.

In patients with bicuspid aortic valves (BAV) there is a nine-fold increase in the risk of developing acute dissections when compared to patients with normal aortic valves. Aortic aneurysms and dissections occur irrespective of altered hemodynamics or age.[70] In contrast to Marfan syndrome, aortic root dilatation in BAV patients is generally located in the ascending aorta, above the sinuses of Valsalva.[71] Even young children with BAV have aortic root dilatation when compared to controls.[72,73] Notably, the process of progressive dilatation of the ascending aorta continues after valve replacement. Patients with BAV require continuous surveillance to treat associated lesions and prevent complications.

Bicuspid Aortic valve may occur sporadic or familial.

The minimal frequency of familial occurrence of bicuspid aortic valve ranges between 9.1% and 17.1%.[74,75] Analysis of these families indicated that the condition is inherited in an autosomal dominant manner with reduced penetrance.

Dietz and colleagues performed a comprehensive evaluation of multiple pedigrees segregating BAV with

ascending aortic aneurysm which revealed a high incidence of individuals with ascending aneurysm alone, suggesting that BAV and ascending aortic aneurysm are primary manifestations of a single gene defect with variable expression.[76] Similar observations of isolated aortic aneurysm formation in family members of patients with BAV were reported by Loscalzo et al.[77] Based on these findings, it is recommended that all family members, including those without BAV require follow-up using imaging protocols that specifically assess aortic segments beyond the sinotubular junction.

Aortic aneurysms with cutis laxa

Cutis laxa is an acquired or inherited condition characterized by redundant, pendulous and inelastic skin. Both autosomal dominant and autosomal recessive forms have been described. Underlying genetic defects are found in the elastin gene (ELN) and the fibulin 5 gene. Until recently, it was believed that the dominant form was free of grave systemic lesions and was associated with a normal lifespan.[78] However, recent observations by Szabo et al. revealed the presence of an aortic aneurysmal phenotype ranging from mild dilatation to severe aortic root aneurysm or aortic rupture in a family and a young girl with sporadic cutis laxa due to a mutation in the ELN gene.[79] Aortic aneurysms were located at the sinuses of Valsalva.

Acknowledgments

Julie De Backer and Bart Loeys are supported as Senior Clinical Investigators by the Fund for Scientific Research - Flanders and Anne De Paepe is recipient of a Methusalem research grant from the Flemish Government and Ghent University.

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