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Review

Current insights in diagnosis and management of the cardiovascular complications of Marfan's syndrome

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Abstract Marfan's syndrome is an inherited disorder of connective tissue, caused by mutations in the fibrillin-1 gene located on chromosome 15. Diagnosis is still based on a combination of major and minor clinical features. Prognosis is mainly determined by the cardiovascular complications. Advances in surgical and medical treatment for these complications have dramatically improved the prognosis of the syndrome.

Keywords: Aortic aneurysm; aortic dissection; survival

MARFAN'S SYNDROME IS AN AUTOSOMAL dominant inherited disorder of connective tissue, with variable complications manifested primarily in the skeletal, ocular, and cardiovascular systems.[1] The estimated prevalence is 2 to 3 incidences per 10,000 of the population.[2] Up to one-third of cases are caused by sporadic mutations.[3] Prognosis is mainly determined by progressive dilation of the aortic root, potentially leading to type A aortic dissection and rupture, these being the major causes of death.[1,4] In this review, we discuss the historical evolution, difficulties in diagnosis, and cardiovascular complications of the syndrome. We also describe the strategies for clinical management, outcomes of surgical intervention, and overall survival.

History

The syndrome is named after the French paediatrician, Antoine Marfan, who first described the skeletal features of the disorder in 1896.[5] He referred to the condition as dolichostenomelia, meaning long and thin limbs. The association of an ectopic location of the lens was reported in 1914,[6] and the autosomal dominant mode of inheritance was recognized in 1931.[7] Aortic dilation and dissection were both first described in 1943.[8,9] More recently, prolapse of the mitral valve and dural ectasia were described in patients with the syndrome.[10,11] Major advances in therapy, such as cardiovascular surgery to replace the dilated aortic root,[12] and the use of β-adrenergic blockade to reduce the rate of aortic dilation and aortic dissection,[13] were made during the 1980s and 1990s. In 1991, the association with the fibrillin-1 gene was discovered.[14]

Molecular diagnosis

The diagnosis of the syndrome is based on a system of clinical features with both major and minor criterions, as classified in 1996 by consensus of a team of experts.[15,16] This is the so-called Ghent nosology (Table 1). For diagnosis, it is necessary to satisfy major criteria in at least two different systems of organ, and to recognize involvement of a third system.

In 1991, Dietz et al.[14] showed that mutations in FBN1, the gene that encodes for fibrillin-1, carried at locus 15q21 on the long arm of chromosome 15, produce the syndrome. Fibrillin-1, a 350 kDa glycoprotein, was discovered in 1986 as the main component of extracellular microfibrils.[17] Microfibrils act as a scaffolding for the formation of elastic fibers, and contribute to the mechanical function of the elastic fibers in the extracellular matrix of connective tissue.[18,19] After discovery of the mutation, it was hoped that the absolute criteria for the syndrome

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Table 1. Diagnostic criteria for Marfan's syndrome.

Category	Major criteria	Minor criteria
Family history	Independent diagnosis in parent, child, sibling	None
Genetics	Mutation FBN1	None
Cardiovascular	Aortic root dilation Dissection of ascending aorta	Mitral valvar prolapse calcification of the mitral valve (<40 yrs) Dilation pulmonary trunk Dilation/dissection of descending aorta
Ocular	Ectopic lens	(2 needed): Flat cornea Myopia Elongated globe
Skeletal	(4 needed): Pectus excavatum needing surgery Pectus carinatum Pes planus Wrist and thumb sign Scoliosis >20° or Spondylolisthesis Arm span-height ratio >1.05 Protrusio acetabulae (X-ray, MRI) Siminished extension elbows (<170°)	(2–3 major, or 1 major and 2 minor signs): Moderate pectus excavatum High narrowly arched palate Typical face Joint hypermobility
Pulmonary		Spontaneous pneumothorax Apical bulla
Skin		Unexplained stretch marks (*striae*) Recurrent or incisional herniae
Central nervous system	Lumbosacral dural ectasia (CT or MRI)	

had been found, but things turned out to be more complex.[20] Because of the large size of the gene, and its extreme intragenic heterogeneity, with more than 200 different mutations having been found, molecular strategies still play a minor role in diagnosis. At present, it is still not possible to find a mutation in every patient. Latest reports show mutations in approximately two-thirds of patients.[21] Clinical variability is even seen among family members carrying an identical mutation in the gene. This indicates that genetic and or environmental factors modify the phenotypic expression.[22]

Moreover, mutations in the gene have also been found in patients who do not meet the criteria for Marfan's syndrome, these mutations being part of another variety of fibrillinopathy, such as the Sphrintzen-Goldberg syndrome, familial arachnodactyly, familial ectopia lentis, and the MASS-phenotype.[19,23–25] If the mutation of the FBN1 gene is known in a patient with Marfan's syndrome, this information can be used for either prenatal or preimplantation diagnosis, and for identifying relatives with the syndrome.[25,26]

Cardiovascular manifestations

In Marfan's syndrome, changes in the wall of elastic arteries primarily involve the media of the aorta. Recent studies in mouse models suggest that fragmentation of the medial elastic network is one of the main determinants of aortic dilation.[27,28] The histopathologic changes in Marfan's syndrome are often described as cystic medial necrosis, even though the "cysts" represent non-cystic medial structural faults, and necrosis is seldom encountered. A better description for the histopathologic changes is medial degeneration.

The histopathologic changes are not specific for the syndrome, and similar alterations have been found in patients with annuloaortic ectasia, bifoliate aortic valves, and tetralogy of Fallot.[29] Besides the aorta, medial degeneration also affects other elastic arteries, but dilation in these arteries is not common except in the pulmonary trunk. Recently, it was shown[30] that the pulmonary trunk, particularly its root, is also dilated in the majority of patients with the syndrome (Fig. 1).

The changes in the aortic wall are associated with increased stiffness of the ascending aorta.[31,32] In our institution,[33] 78 patients with the syndrome, and 23 matched control subjects, underwent magnetic resonance imaging. Distensibility, and the velocity of the flow wave, were calculated at four different levels in the aorta. Decreased distensibility and an increased velocity in the pulse wave, both parameters of increased stiffness, were found in the patients with

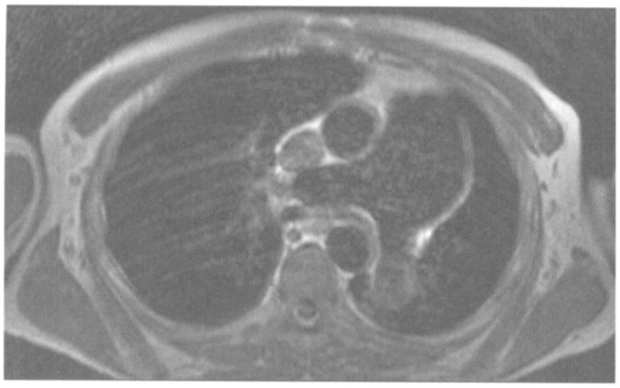
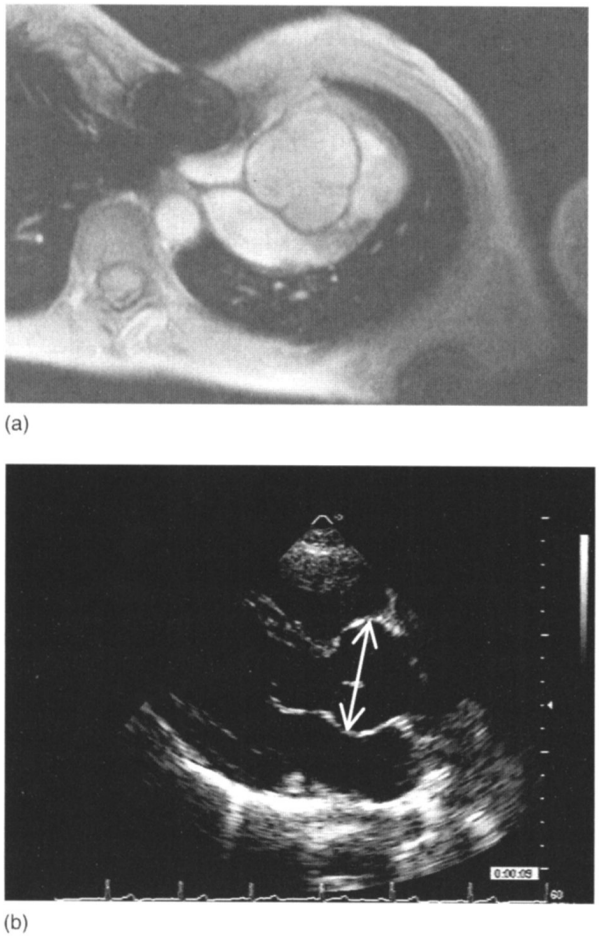


Figure 1.
Resonance image showing dilation of the pulmonary trunk.



(a)

(b)

Figure 2.
These resonance (a) and echocardiographic (b) images show enlargement of the aortic root in a patient with Marfan's syndrome. Note the pectus excavatum and the artefact caused by sternal wires on the resonance image.

the syndrome. The value of aortic elasticity as a risk factor for dissection, however, is yet to be established.

Dilation of the sinuses of Valsalva is found in up to four-fifths of adults with the syndrome (Fig. 2). Elastic fibers, composed of elastin deposited in microfibrils, are relatively more prevalent in the ascending aorta than in any other region of the arterial tree.[34] This biochemical feature, coupled with the repetitive stress of left ventricular ejection, probably accounts for the dilation, which occurs primarily in the aortic root.[10,35–38] The rate of dilation is heterogeneous and unpredictable.[39,40]

Echocardiography in the parasternal long-axis view is used for measurement of the aortic root. According to Meijboom et al.,[41] cine-resonance imaging is also well suited to assess dilation of the aortic root, in particular asymmetric dilation, which might play a role in unexpected dissection of the root in patients with the syndrome.

For children with the syndrome, a frequently used nomogram relating the diameter of the sinuses of Valsalva to body surface area was provided by Roman et al.[42] Recently, Rozendaal et al.[43] developed an adjusted nomogram for screening the population, because children referred for screening are usually taller and thinner, and have a relatively larger body surface area. In adults, correlations are not as high because body surface area is more often disturbed by obesity.[42] In adults, therefore, an upper limit for the normal diameter of the aortic root of 37 to 40 mm is used.

The acute onset of sharp pain between the shoulders, in the anterior part of the chest, or in the neck is the typical presenting symptom of aortic dissection, but some patients are unaware of suffering a dissection. Dissection or rupture of the ascending aorta, nonetheless, is the main cause of death. It usually starts with a tear in the intima of the ascending aorta, which progresses antegrade to the iliac arteries. Retrograde progression of this type of dissection is life-threatening because of the risk of rupture into the pericardial cavity, with tamponade or obstruction of the origin of a coronary artery. Emergency surgery is indicated for all dissections of this type, which fall into category A of the Stanford classification. Risk factors for this type of dissection are the size of the aortic root, a rapid rate of increase of dilation, and a family history of severe cardiovascular manifestation.[44–49] The incidence of dissection is higher in patients with generalized as opposed to localized dilation of the aortic root.[38]

Aortic dissection with the origin beyond the left subclavian artery, but without involvement of the ascending aorta, so-called type B in the Stanford classification, can be treated initially with medical therapy (Fig. 3). But, when the descending aorta exceeds 50 mm in diameter, and when there are recurrent symptoms, surgery is indicated.[50] When ischaemia of an organ or limb is evident, aortic fenestration with or without placement of a stent

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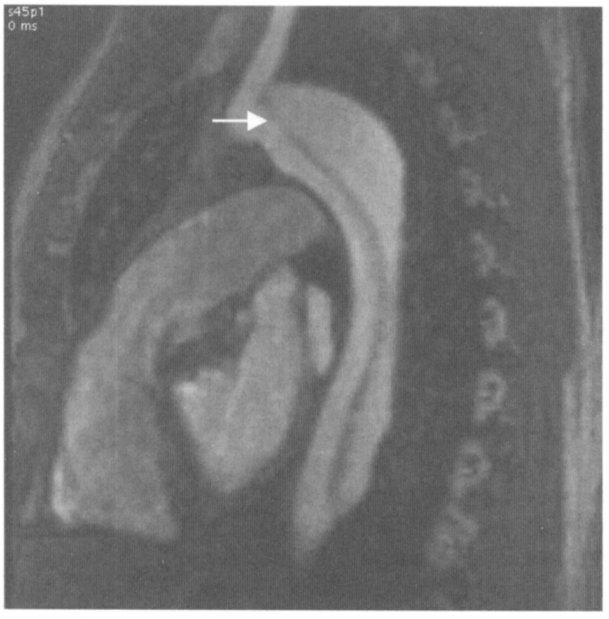

Figure 3.
Resonance image showing dissection of the arch of type B in the Stanford classification (arrow).

can be performed.[51] Less than one fifth of all first acute dissections fit the pattern of type B dissection.[35,52]

The risk of developing aortic regurgitation is related to the aortic diameter, and regurgitation is usually caused by dilation of the aortic sinuses and the sinutubular junction.[53] In adults with the syndrome, aortic regurgitation is uncommon when the maximal diameter of the aortic root is from 45 to 50 mm, but is almost invariably present when the aortic root exceeds 60 mm in diameter.[54] As with aortic regurgitation not due to Marfan's syndrome, valvar replacement is indicated if there is an increase in end-systolic left ventricular dimension, a decrease in ejection fraction, and/or if there are symptoms attributable to the regurgitation.[55]

In many patients, the earliest clinically evident changes occur in the mitral valve. Prolapse of this valve is present in approximately four-fifths of all patients.[54,56] The prevalence of prolapse increases with age, and this is more common in women. In more than a quarter of patients with prolapse, substantial mitral regurgitation develops, necessitating surgery by conservation of the valve or replacement with a mechanical prosthesis.[54] Calcification of the annulus accompanies prolapse in an unusually high proportion of patients with the syndrome. Stringent criteria for diagnosis of prolapse should be used, including late systolic prolapse over 2 mm on M-mode echocardiography, or billowing of leaflets into the left atrium in the long-axis view on cross-sectional echocardiography.[57]

Pregnancy in patients with the syndrome

For women with the syndrome, pregnancy presents a two-fold problem: first the genetic problem, since there is a one in two chance that the child will be affected and, second, that there will be progression of pre-existing cardiovascular problems, such as mitral regurgitation, aortic regurgitation, and dilation of the aortic root. Dilation, should it occur, will increase the risk of dissection during or shortly after pregnancy. Three important studies reported more than 160 pregnancies in patients with the syndrome.[58–60] In these studies, it became apparent that the risk for aortic dissection was low in women with minimal cardiac involvement and a diameter of the aortic root less than 40 mm.

Currently, it is recommended that women with a diameter of the aortic root beyond 45 mm should be strongly discouraged from becoming pregnant unless they undergo elective replacement of the root before becoming pregnant. With diameters between 40 and 45 mm, we recommend an individual approach, based on growth of the aortic root and family history. When the aortic diameter is below 40 mm, then problems are rare, although a completely safe diameter does not exist.[61]

Patients with severe kyphoscoliosis and restrictive lung disease obviously have a higher risk, both at operation and during pregnancy. This should be taken into account when counselling patients before pregnancy and elective surgery.

Marfan's syndrome in the neonate

Neonates with Marfan's syndrome represents the most serious end of the spectrum of the disease. Presentation is characterized by massive mitral and tricuspid valvar insufficiency, leading to congestive heart failure, failure to thrive, pulmonary hypertension, and death shortly after birth. This is not a separate entity, but a form of the syndrome caused by specific mutations of fibrillin-1 in exons 24–27 and 31–32.[62]

Medical management

The notion that β-adrenergic blockade protects the aorta in patients with the syndrome from both dilation and dissection originated three decades ago.[63] Multiple studies have confirmed the expected beneficial effect of propranolol or atenolol, both in adults[13,40] and children.[64] The effects believed to slow down the process of dilation and dissection comprise the decrease in heart rate, and thus less fatiguing stress cycles, lowering of dp/dt, and lowering of the blood pressure.

The study of Shores et al.[13] demonstrated a significant decrease in rate of aortic dilation and a small

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improvement in survival in patients randomized to β-blockers during a follow-up of more than 10 years. Data from Silverman et al.[65] endorsed these conclusions. Silverman et al.[65] also suggested that surgery alone could not explain the total observed increase in survival, and that medical therapy also contributed to the benefit.

Changes in distensibility, and in the velocity of the pulse wave, parameters for elasticity, were studied in our institution along the entire aorta using resonance imaging. These studies further showed that β-blockade reduced aortic stiffness and mean blood pressure.[66]

Some studies suggested that certain patients might be more responsive to β-adrenergic blockade than others.[48,67] This heterogeneous response probably reflects increased peripheral vascular resistance due to β-blockade, which can be reduced substantially by concurrent vasodilator therapy. Treatment starts with a low dose, which is gradually increased until the resting heart rate is approximately 60 beats per minute. Maximal heart rate should not exceed 100 beats per minute during submaximal exercise.[35]

In addition to reducing aortic stress by pharmacological means, it is advisable to avoid physical exercise. In particular, patients should be strongly recommended to avoid contact and isometric sports.[68]

Indications for surgical intervention

Because of the excellent results of elective replacement of the dilated aortic root with a composite graft in the Bentall procedure,[12] or with a valve-sparing procedure,[69,70] thresholds for an elective procedure have continuously been lowered in the past decades.

At present, guidelines for elective replacement of the aortic root include:[61]

- A maximal diameter of the root greater than 55 mm.
- A maximal diameter greater than 50 mm in patients with a family history of dissection, with rapid increasing diameter of more than 2 mm per year, or with severe aortic regurgitation requiring surgery.
- A maximal diameter of greater than 45 to 50 mm if an operation is planned to spare the aortic valve, or if pregnancy is desired.

These guidelines were considered retrospectively in 13 patients with the syndrome who had developed dissection of the root over a period of 14 years.[46] Had the guidelines been available earlier, and followed, then the dissection could have been prevented in 11 of the patients.

Aortic surgery

Surgery should be performed in a specialised centre, and by surgeons with substantial experience with the required maneuvers. The surgical options for replacement of the aortic root are:

- A composite graft repair, in other words the modified Bentall procedure, using a mechanical, bioprosthetic, or homograft valvar prosthesis.
- A procedure designed to spare the aortic valve.

It was in 1968 that Bentall and DeBono[12] described the procedure in which the aortic root and ascending aorta were replaced with a tubular Teflon graft containing a mechanical valvar prosthesis. The coronary arteries were reimplanted in the graft. It is a modification of this procedure that has now became the standard operation for patients with aneurysm of the aortic root in the setting of Marfan's syndrome.[71] In 1992, David and Feindel[69] described a method for reconstruction of the aortic valve in patients with aneurysmal roots whereby the three sinuses of Valsalva and the ascending aorta were excised and the valve itself was re-implanted inside a tubular Dacron graft. This approach, and other procedures which spare the native valve, are alternatives to the Bentall procedure when the aortic valvar leaflets are macroscopically normal.[72] Such valve-sparing procedures, however, cannot be used when the sinuses are widely dilated, or when the leaflets of the valve are markedly stretched. Valve sparing, therefore, is not recommended for those patients with aortic roots wider than 50 mm.

Many surgeons believe that valve-sparing operations should not be used in patients with the Marfan's syndrome because of concern that the hinge points of the leaflets will themselves dilate subsequent to the procedure. Fleisher et al.[73] found a high degree of structural deterioration of leaflets excised from patients during replacement of the aortic root even when the leaflets themselves appeared normal. On the other hand, Yacoub et al.[74] argued that the valve should be preserved whenever possible because of the many advantages of retaining the native structure, including maintenance of the extremely sophisticated dynamic structure of the aortic outflow tract, and the lack of need for anticoagulation.

Outcomes of surgery

In our population, a significantly better 10-year survival was found in those patients in whom the aortic root had been replaced electively compared to those requiring an emergency repair for aortic dissection. The results were striking, with survival of 97% versus 31%.[46] In a more recent report,[71] operative

mortality was 1.5% for elective operations, and 11.7% for emergency operations. Survival for five and ten years after elective replacement of the aortic root was 84%, and 75%, respectively. Another recent study[75] has reported survival of all selected patients at 5 years following elective surgery designed to spare the aortic valve. After replacement of the aortic root, patients deserve continued attention because of complications that may eventually develop in the ascending aortic beyond the aortic root.[52,76] Replacement of the root is associated with a considerably higher risk of redissection and recurrent aneurysm than in those patients with aortic disease of different aetiology.[77] Presence of dissection, either acute or chronic, at the time of the first operation was a significant predictor of subsequent need for reoperation.[52] Other risk factors for reoperation were hypertension and smoking.

In our institution, Meijboom et al.[78] reported that almost half of our patients had aneurysms of the orifices of the coronary arteries after elective replacement of the aortic root. They concluded, however, that this complication, although common especially in those patients younger than 35 years at the time of surgery, probably carried a low risk after elective surgery.

Survival

Before the era of open-heart surgery, the majority of patients with Marfan's syndrome died prematurely of rupture of the aorta, often by the third decade of life.[79] Cardiovascular complications were the cause of death in more than nine-tenths, with aortic rupture accounting for four-fifths of deaths. Life expectancy has increased significantly in the past three decades. In 1995 Silverman et al.[65] reported a median survival of 72 years, compared to 48 years in 1972. Similarly, Finkbohner et al.[52] found that, after surgical repair of aortic aneurysms, the median age at death of their patients in 1995 was 61 years.

Follow-up

Whenever possible, patients with the syndrome should be under the care of professionals with specific training and experience. Ideally, this should be performed in a multidisciplinary setting. All patients with Marfan's syndrome are advised to take β-adrenergic blocking agents, and to remain on this therapy unless intolerable side effects preclude their use. This is especially true, usually in association with other blood pressure lowering agents, if dissection has occurred. During follow-up, the aortic root and the entire aorta should be regularly evaluated with echocardiography, magnetic resonance imaging, computed tomography, and/or abdominal ultrasound examinations, especially if a dissection remains and its stability is being monitored. Patients with mitral valvar prolapse, and more than moderate mitral regurgitation, should also be followed with yearly echocardioraphic examinations. Prophylaxis against endocarditis is recommended for 6 months following replacement of the aortic root, or for life if any residual gradient or lesions persist, or in the presence of prosthetic valvar or mitral regurgitation.[61]

Conclusion

Life expectancy has increased significantly in patients with Marfan's syndrome, due to advances in medical and surgical treatment. In an unknown number of patients, nonetheless, diagnosis is only established after development of an aortic aneurysm, dissection, or even after death. Early diagnosis, therefore, should be improved by increased awareness in the general population and education of physicians. Because aortic complications are not always predictable exclusively on the basis of dimensions of the aortic root, further research should focus on the functional properties of the aorta, and molecular genetics to identify the patients at greatest risk for aortic dissection.

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