Multidisciplinary approach to a Marfan syndrome patient with emphasis on cardiovascular complications

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Background. Marfan syndrome (MFS) is the most common inherited disorder of connective tissue affecting multiple organ systems. The most life-threatening and life-shortening complication is aortic dissection. Without surgery, life expectancy of MFS patients is reduced to approximately 32 years. Early identification and appropriate multidisciplinary medical cooperation is essential.

Conclusion. Proper follow up, therapy and timely surgical repair lead to an almost normal lifespan in affected individuals.

Key words: Marfan syndrome, aneurysms, aorta, aortic dissection, cardiovascular complications

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INTRODUCTION

Marfan syndrome (MFS) is the most common autosomal-dominant disorder of connective tissue. It was originally described by Dr. Antoine Marfan in 1896. Its incidence is approximately 2-3 per 10,000 individuals without gender or ethnic predilection. It involves many systems but the most prominent manifestations are of skeletal, ocular and cardiovascular origin¹. Aortic dilation and dissection are the major causes of morbidity and mortality². The life expectancy of untreated patients with MFS is reportedly reduced to about 32 years. Early diagnosis and appropriate multidisciplinary management are therefore key factors in the prognosis of MFS patients who are prone to life-threatening cardiovascular complications. Clinical genetics, cardiology and cardiac surgery are among the most involved specialties.

Genetic basis and pathology

The first genetic mutation connected to MFS was reported in 1991. This maps to the 15q21 chromosome where the defective gene for fibrillin-1 (FBN1) is allocated. Fibrillin-1 is a main component of microfibrils which form the elastic tissue of aortic media. FBN1 gene mutations increase the susceptibility of elastic fibers to proteolysis and tissue fragility (cystic medionecrosis – histological marker of MFS). These histological changes lead to stiffer and less distensible aortic walls³. More than 500 mutations of FBN1 have already been found. The mutation in approximately 75% of cases is directly inherited from affected parent while the remaining cases are de novo mutations. Despite progress in molecular genetics, there is little correlation between FBN1, clinical phenotype and prognosis and hence genetic counseling is of paramount importance.

Genetic counseling

Because of genetic error in microfibril design, several

organ systems are involved (mainly cardiovascular, skeletal, ocular). A comprehensive multidisciplinary approach known as Ghent criteria was proposed in 1996 for MFS patient selection⁴. The diagnosis requires careful physiognomy examination combined with medical and family history information.

In the absence of family history of MFS, the diagnosis is made by identifying major criteria in two different organ systems and involvement of a third system or in the presence of FBN1 mutation and major criteria in one organ system and involvement in a second organ system.

In the presence of a family history of MFS in a first-degree relative who meets major criteria independently, the diagnosis of MFS can be made from one major criterion in one organ system and involvement of a second organ system.

The skeletal manifestations of MFS make it easy for the clinical geneticist to measure arm span to height ratio, upper to lower segment ratio as well as scoliosis, pectus deformity, high arched palate, joint hypermobility and degree of elbow extension.

The ocular manifestation of MFS – myopia, glaucoma and retinal detachment caused by lens dislocation and found in around 60% of patients is diagnosed by an ophthalmologist.

There are other syndromes with aortic dissection risk which must be taken into account in the differential diagnosis:

- Ehlers-Danlos syndrome
- Loeys-Dietz syndrome (mutation in TGFBR1 gen) (ref.⁵)
- Familial thoracic aortic aneurysm (patients without physiognomy of MFS) (ref.⁶)
- MASS phenotype (Mitral valve prolapsed, Aortic root enlargement, Stretch marks of the skin, Skeletal conditions like MFS)
- Bicuspid aortic valve

Table 1. Genetic syndromes with aortic dissection risk.

Name	Gene	Chromosome	Inheritance pattern	Features common with MFS
Ehlers-Danlos syndrome	Collagen (COL3A1)	2	Autosomal dominant	Rupture of large arteries
Loeys-Dietz syndrome	Transforming growth factor beta receptors (TGFB1, TGFB2)	3, 9	Autosomal dominant	Cardiovascular and skeletal (ref. ⁵)
Familial thoracic aortic aneurysm	Unknown	3, 5, 11	Autosomal dominant ?	Thoracic aorta aneurysm and dissection (ref. ⁶)
MASS phenotype (Mitral valve prolapse, Aortic root enlargement, Stretch marks of skin, Skeletal conditions like MFS)	FBN1	15	Autosomal dominant	Cardiovascular, skeletal and skin
Bicuspid aortic valve	Unknown	Not mapped	Autosomal dominant ?	Dilatation and dissection of ascending aorta

If MFS is diagnosed, periodic clinical genetics consultation is highly recommended to discuss hereditary and potential pregnancy implications.

Cardiology

The major cause of morbidity and mortality in MFS are cardiovascular complications due to aortic dissection or direct rupture leading to premature death. Without early recognition of aortic aneurysmatic dilation and prophylactic surgery, approximately 50% of MFS patient die by the age of 40 (ref.⁷). Dilation of the ascending aorta is found in 50% of adults with MFS.

Echocardiography is the most accessible modality for aortic dilation assessment. Risk factors for aortic dissection in MFS include the following:

- aortic root diameter > 5cm
- progressive aortic dilation beyond the sinuses of Valsalva
- rapid rate of aortic dilation (more than 2mm per year)
- family history of aortic dissection

Owing to body size differences, to measure the aortic diameter, the body surface area of the MFS patient should be taken into account. Patients with an aortic diameter less than 2.75 cm/m² are probably at low risk of dissection, 2.75 - 4.24 cm/m² are at moderate risk and patients with an aortic diameter greater than 4.25 cm/m² are at high risk. Increased aortic stiffness can be measured by M-mode echocardiography and Doppler tissue imaging. The aortic stiffness index has been reported to be a predictive factor for dissection⁸.

Aortic valve regurgitation and mitral valve prolapse are another manifestation of MFS. Pulmonary artery dilation can be also found but this does not normally lead to any clinical symptoms.

Other imaging modalities such as computer tomography and magnetic resonance are also feasible especially for whole aorta scans (aortic arch, descending aorta). Dilation of the descending aorta is another risk factor and complication of MFS (ref.⁹).

Serial measurement of the aortic root is important for evaluating the progression of dilation and proper surgical

treatment timing. Recommendations are as follows: diameter less than 4.5 cm – echocardiography once per year, diameter more than 4.5 cm – echocardiography twice per year.

For reduction of aortic dilation and stiffness, beta-blockers are recommended in all MFS patients. The desired mechanism is by lowering heart rate and ejection force. Several studies have shown a reduced rate of aortic dilation in beta-blocked patient groups¹⁰. The dose should be adjusted for a resting heart rate of 60-70 beats/min and blood pressure less than 120/80 mmHg. Beta-blockers should be continued indefinitely unless not tolerated. In MFS patients intolerant to beta-blockers calcium channel blockers is an option. In a very small randomized trial an ACE-I (perindopril) reduced aortic root diameter¹¹. Angiotensin receptor blocker (losartan) also demonstrated some promise in aortic dilation reduction. Pharmacological treatment unfortunately does not prevent aortic complications (dissection).

Because of pronounced blood pressure fluctuation MFS patients should avoid contact sports and demanding physical activity.

Cardiac surgery

Dilated ascending aorta replacement is the only way for preventing deadly complications of MFS – aortic rupture or dissection. In general, prophylactic surgery is recommended when the diameter of the ascending aorta at the level of aortic sinuses reaches 5.0 cm (ref.¹²). Normal values indexed for body surface area should be applied¹³. Several factors suggest an even earlier surgical intervention (diameter of aorta less than 5.0 cm):

- family history of dissection
- increased speed of aortic dilation (> 2 mm/year)
- severe aortic valve regurgitation with left ventricular dilation
- aortic valve-sparing surgery feasibility

The standard surgical approach for the majority of MFS patients is the Bentall procedure introduced in 1968. Composite aortic root conduit consists of woven graft connected with mechanical prosthesis. Dilated ascending

aorta and root are removed and replaced with conduit with coronary artery reimplantation. Current mechanical prostheses have superb flow parameters, but their proper function demands lifelong anticoagulation. Bentall procedure has very low mortality and predictive long term outcome. It has been demonstrated by several studies that actuarial freedom from thromboembolism, endocarditis and reoperation in the residual aorta 20 years postoperatively is 93, 90 and 74% (ref.¹⁴).

Some patients have medical contraindications that make anticoagulation hazardous. In these circumstances, aortic root and valve can be replaced by conduit with bovine or porcine bioprosthesis. The durability of these xenografts is limited to approx. 10-15 years. Later, the risk of reoperation is not negligible – sternal re-entry can endanger right ventricle with massive bleeding, coronary ostia buttons has to be reimplanted, xenograft can be heavily calcified and native annulus scarred down.

Another option for avoiding anticoagulation is valve-sparing aortic root replacement. Several types of these operations had been described, but there are two basic concepts. The “Remodeling” procedure pioneered by Yacoub in 1979 involves resection and replacement of the sinuses of Valsalva and coronary artery reimplantation. A later procedure called “reimplantation” was described by David in 1988 and involves reimplantation of the native aortic valve into Dacron graft. “Remodelling” approach’s physiological advantage is that the scalloped graft billows and mimicks the natural sinuses of Valsalva. The latter has the theoretical advantage of stabilizing the aortic annulus, which can predispose to postoperative annular dilation and recurrent aortic regurgitation. Both techniques require reimplantation of the coronary ostia into Dacron graft. The last improvement of “reimplantation” technique consists in using larger graft size which is “necked down” at the bottom end to create pseudosinuses. Advantages of both techniques were suggested by Lansac: remodelling procedure with sinus preservation and external annuloplasty ring implantation for aortic annulus stabilization¹⁵. In valve-sparing surgeries one should take into account the quality and shape of aortic valve leaflets. Patients with prolapsed or stretched cusps can have successful repair by plication techniques¹⁶. Even though valve-sparing techniques are safe and reproducible, outcomes are not perfect. At 10 years, approximately 25% of MFS patients undergoing valve-sparing surgery had severe aortic regurgitation¹⁷. There persists a question if the overall incidence of valve-related and aorta-related complications is lower than that after conventional mechanical Bentall conduit. An MFS patient who chooses a valve-sparing type of operation should understand that a second surgery may be necessary in future.

The incidence of dissection in the residual arch after aortic root replacement is extremely low and therefore prophylactic replacement of aortic arch is not generally recommended¹⁸.

Mitral valve regurgitation occurs in approximately 50% MFS patients. In the largest series of aortic root replacement only 10% required concomitant mitral valve

surgery. Mitral valve repair is a tempting option especially when valve-sparing procedure is accomplished. When classical mechanic prosthesis Bentall procedure is performed mitral valve replacement rather than repair is considered.

Descending aorta dilation and dissection is less common in MFS patients. Initial treatment of patients with acute B dissection is in the absence of organ malperfusion is pharmacological (arterial pressure correction, anti-impulse therapy). Data on stent-grafts in patients with MFS or other connective tissue disease are very limited and therefore application of these devices is mostly contraindicated. There is general agreement on descending aortic replacement in chronic dissection when the diameter of the aorta exceeds 6.5 cm or rate of growth is more than 0.5 cm/6 months. Mortality in type B acute dissection when surgery is performed exceeds 30%.

After surgery, it is necessary to continue monitoring the remaining aorta in MFS patients for the rest of their lives. Echocardiography, computer tomography or magnetic resonance imaging are usually indicated once per year.

Gynecology

Having an off-spring is a natural wish of a human being. Even with the potential severe cardiovascular risk of MFS patient pregnancy is possible. Optimum care for patients with MFS requires adequate preconceptional counseling and multidisciplinary approach to pregnancy, delivery and in the postpartum period. There are two major aspects to discuss with patient and family: increased risk of cardiovascular complications and 50% chance (autosomal-dominant way of inheritance) of transmission of MFS to the child.

The higher risk of aortic dissection during pregnancy is due to hyperdynamic blood circulation and hormonal influence of elastin and collagen fibers in aorta. Before pregnancy, magnetic resonance imaging of whole aorta should be performed. Proper echocardiographic monitoring of ascending aorta during all phases of pregnancy is of the utmost importance. The risk of complications is increased when root diameter is >4 cm and there is rapid dilation detected during pregnancy. Further, more than 40% of pregnancies had neonatal complication either (premature delivery because of premature rupture of membranes, cervical incompetence) (ref.¹⁹).

There is no consensus about mode of delivery in women with MFS. Assisted vaginal delivery can be considered when the aortic diameter is < 4 cm and there is no dilation during pregnancy. Because of rise in blood pressure, uterine contractions, amount of pain and anxiety, Caesarean section is usually indicated and performed.

After delivery, higher cardiovascular risk decreases to MFS patient values slowly and the patient should be carefully monitored. Type A and B aortic dissection has occurred in close postpartum period even in the absence of preexisting aortic enlargement²⁰. Molecular analysis of a newborn should be performed for MFS inheritance detection and proper further care and monitoring.

Ophthalmology

The main ocular features of Marfan syndrome, all of which can result in decreased vision, include ectopia lentis (lens dislocation), myopia and retinal detachment. About 50% of patients with MFS are diagnosed by an ophthalmologist because individuals may present with isolated ocular signs suggestive of this syndrome. Diagnostics approach includes routine examination of refraction, intraocular pressure measurement, and evaluation of the peripheral retina and optic nerve head. Recent advances in diagnosis, together with improved surgical techniques for the repair of ocular complications have contributed to the preservation of sight in these patients²¹.

Orthopedics

Because of the skeletal manifestations, orthopedic specialist can sometimes be the first to diagnose patient with MFS. Joint laxity, pectus deformations, chronic subluxation of patella and shoulder, genu valgum, pes planovalgus and arachnodactyly are common. Scoliosis occurs in over 60% of patients and is most often thoracic and convex to the right. Protrusio acetabuli (found in 20% of MFS patients) can cause reduced range in hip motion. Symptoms suggestive of dural ectasia include back pain, headache, proximal leg pain, weakness and numbness above the knee, and genital or rectal pain.

CONCLUSION

The Marfan syndrome is a heritable connective tissue disorder with multisystem involvement and variable expression of signs and symptoms, caused by mutations within the fibrillin gene. Although many mutations have been found, genotype-phenotype correlations for determining clinical consequences and risks must be investigated in future. The most life-threatening complication is thoracic aortic aneurysm formation, dissection and rupture. Early recognition can be lifesaving for the affected individual and family members. Early diagnosis and complex management requires the cooperation of variety of medical specialists. With proper therapy and elective surgical repair, the median cumulative probability of survival has increased to over 72 years².

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