The Marfan Syndrome

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Key words: Marfan syndrome, FBN1 gene, fibrillin-1, ectopia lentis, kyphoscoliosis, aortic tear, dural ectasia

IMAJ 2008;10:175–178

In 1955 McKusick introduced a novel class of diseases he named "disorders of connective tissue" [1]. Marfan syndrome, first reported in 1896, is probably the best known example of these disorders, which comprise today over 200 distinct conditions. In recent years it became apparent that what was once known as Marfan syndrome is in fact a group of related disorders caused by several different genes of which FBN1 can serve as a paradigm.

The inheritance of Marfan syndrome is autosomal dominant with complete penetrance but with considerable clinical variability, ranging from mild musculoskeletal or ocular manifestations to severe neonatal presentation. In view of the broad clinical spectrum of the disease, the term microfibrillopathies has been suggested to describe the full spectrum of clinical manifestations. The estimated prevalence of Marfan syndrome is one in 5–10,000 [2]. There is no gender preference and no ethnic predisposition.

History

In 1896, Antoine-Bernard-Jean Marfan reported the case of a 5 year old girl with long limbs, digital and joint contractures, and kyphoscoliosis [3]. Although this patient could have had contractural archnodactyly (Beals syndrome), Marfan's name has been used to denote the combination of symptoms associated with defects in the gene FBN1.

Involvement of the aorta was recognized only in 1943 [4], and the role of aortic dilatation in shortening the life expectancy was clarified in 1972 [5]. The role of fibrillin in the pathogenesis was demonstrated by Hollister et al. in 1990 [6], and the disease locus was subsequently assigned to chromosome 15q21.1 [7]. Proof that mutations in the fibrillin-1 gene (FBN1) can cause Marfan syndrome was provided by Dietz et al. in 1991 [8].

Molecular basis

In its genomic locus FBN1 is divided into 65 exons and codes for profibrillin-1, a ~350 kD cysteine-rich glycoprotein that undergoes secretion and processing to produce fibrillin-1. Fibrillin displays a modular structure consisting of repeated motifs. The most common motif is the epidermal growth factor precursor-like motif, which occurs 47 times in fibrillin-1. EGF motifs contain six conserved cysteine residues associated by three disulfide bonds. Forty-three EGF modules also contain a calcium-binding sequence (cbEGF). Stretches of cbEGF motifs are interrupted by other modules including seven 8-cysteine modules with homology to latent transforming growth factor-beta binding protein-1 [9].

Pathogenesis

Fibrillin-1 is a main component of a class of 10–12 nm extracellular microfibrils found in a wide range of tissues in association with elastin within elastic fibers, and in elastin-free bundles in tissues such as the ciliary zonule. Microfibrils are thought to be necessary for both the formation of elastic tissues and to elastic properties of tissues themselves. Mutated FBN1 alters the structure of fibrillin-1 or decreases its amount, thus compromising the tensile properties of the microfibrils. In addition, there is evidence suggesting that the abnormal gene product can interfere with the function of the normal fibrillin-1 produced by the non-mutated allele (known as the dominant negative effect), further compromising the mechanical properties of the connective tissue. In addition to its structural function, fibrillin-1 has regulatory and signaling functions that have not yet been fully elucidated.

As detailed above, fibrillin-1 contains seven structural modules of latent TGFβ binding protein 1. Recently it was suggested that deficiency of LTBP is associated with increased levels of the ligand active TGFβ. Increased levels of TGFβ were shown to cause abnormal alveolar septation and mitral valve myxomatosis and to contribute to the dilatation of the aorta in an animal model [10]. This effect was preventable and even reversible by TGFβ antagonists such as losartan [11].

Genotype-phenotype correlations

Missense mutations represent about two-thirds of all FBN1 mutations identified to date, and the majority of these mutations affect one of the 43 cbEGF modules of fibrillin-1, usually leading to a substitution of one of the six highly conserved cysteine residues or of residues of the calcium-binding consensus sequence.

Mutations associated with premature termination codons or affecting splice site consensus sequences with resultant exon skipping are also relatively common.

The neonatal Marfan syndrome represents the severest end of the clinical spectrum of the fibrillinopathies and is associated with mutations in exons 24–32. Affected individuals are

EGF = epidermal growth factor

TGFβ = transforming growth factor-beta
LTBP = transforming growth factor-beta binding protein-1

generally diagnosed at birth or shortly thereafter. Unique features include joint contractures, "crumpled" external ears, and loose skin. Congestive heart failure associated with mitral and tricuspid regurgitation is the main cause of death, while aortic dissection is uncommon. Survival beyond 24 months is rare [12].

At the milder end of the phenotypic spectrum are fibrillinopathies with isolated ectopia lentis and isolated skeletal involvement, or various combinations of these abnormalities but without aortic dilatation. Although specific mutations have been associated with such phenotypes, the mechanisms modifying the clinical presentation are yet to be discovered [13].

Diagnosis

Since Marfan syndrome is a pleiotropic disorder with extensive clinical variability, the diagnosis is not always simple and is based on agreed clinical criteria (Ghent nosology) [14]. These criteria distinguish between major and minor features in the ocular, skeletal, integumental, respiratory and cardiovascular systems [Table 1]. Major criteria in two systems combined with involvement of a third system are required for the unequivocal diagnosis in a sporadic case, while in familial cases the criteria are less stringent and require a single major criterion. Demonstration of a mutation in the Marfan syndrome gene FBN1 by itself is sufficient for diagnosis in a familial context.

Ocular manifestations

Refractive errors, such as myopia and astigmatism, are the most common ocular findings, but only ectopia lentis, seen in about 60% of patients, is a major feature. Marfan patients have increased risk for retinal detachment, glaucoma and early cataract formation.

Table 1. Diagnostic criteria for the Marfan syndrome (Ghent nosology)

Skeletal System

Major criteria: Presence of at least four of the following manifestations:
- Pectus carinatum
- Pectus excavatum requiring surgery
- Reduced upper to lower segment ratio or arm span to height ratio > 1.05
- Positive wrist and thumb signs
- Scoliosis of > 20° or spondylolisthesis
- Reduced extension of the elbows (< 170°)
- Medial displacement of the medial malleolus causing pes planus
- Protrusio acetabulae of any degree (ascertained on X-ray)

Minor criteria:
- Pectus excavatum of moderate severity
- Joint hypermobility
- Highly arched palate with dental crowding
- Facial appearance (dolicocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)

For the skeletal system to be involved, at least two of the components comprising the major criterion, or one component comprising the major criterion plus two of the minor criteria must be present.

Ocular System

Major criterion:

Ectopia lentis

Minor criteria:
- Abnormally flat cornea (as measured by keratometry)
- Increased axial length of globe (as measured by ultrasound)
- Hypoplastic iris or hypoplastic ciliary muscle causing a decreased miosis

For the ocular system to be involved, at least two of the minor criteria must be present.

Cardiovascular System

Major criteria:
- Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva, or
- Dissection of the ascending aorta

Minor criteria:
- Mitral valve prolapse with or without mitral valve regurgitation
- Dilatation of main pulmonary artery, in absence of valvular or peripheral pulmonic stenosis or any other obvious cause, under the age of 40 years
- Calcification of the mitral annulus below the age of 40 years, or
- Dilatation or dissection of the descending thoracic or abdominal aorta below the age of 50 years

For the cardiovascular system to be involved, a major criterion or only one of the minor criteria must be present.

Pulmonary System

Major criteria:
- None

Minor criteria:
- Spontaneous pneumothorax, or
- Apical blebs (ascertained by chest radiography)

For the pulmonary system to be involved, one of the minor criteria must be present.

Skin and Integument

Major criterion:
- Lumbosacral dural ectasia by computed tomography or magnetic resonance imaging

Minor criteria:
- Striae atrophicae (stretch marks) not associated with marked weight changes, pregnancy or repetitive stress, or
- Recurrent or incisional herniae

For the skin and integument to be involved, the major criterion or one of the minor criteria must be present.

Family History

Major criteria:
- Having a parent, child, or sibling who meets the diagnostic criteria listed below independently
- Presence of a mutation in FBN1 known to cause the Marfan syndrome, or
- Presence of a haplotype around FBN1, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family

Minor criteria:
- None

For the family history to be contributory, one of the major criteria must be present.

Requirements for the diagnosis of Marfan syndrome

For the index case:
- Major criteria in at least two different organ systems and involvement of a third organ system

For a family member:
- Presence of a major criterion in the family history and one major criterion in an organ system and involvement of a second organ system

Musculoskeletal manifestations

The extremities are disproportionately long for the size of the trunk, and patients are usually tall. Overgrowth of the ribs can deform the chest wall causing pectus excavatum or pectus carinatum. Scoliosis is common and can be progressive. Acetabular protrusion and joint laxity are other skeletal manifestations.

Cardiovascular system

Cardiovascular manifestations include dilatation of the aorta at the level of the sinuses of Valsalva, and predisposition for aortic tear and rupture. These severe complications are the major cause of morbidity and mortality and are the central target for therapy. Mitral valve prolapse, triscuspid valve prolapse, and enlargement of the proximal pulmonary artery are other common but minor criteria for diagnosis.

Integumental manifestations

Skin stretch marks (strie) in the absence of rapid weight gain and recurrent hernias are common minor manifestations.

Dural ectasia

Progressive lumbosacral dural ectasia (stretching of the dural sac) is a major diagnostic criterion. This age-dependent feature is present in 92% of patients (average age 26 years) [15]. Dural ectasia is usually asymptomatic but can lead to bone erosion and nerve entrapment, resulting in low back pain and proximal leg pain, weakness and numbness. Dural ectasia is the second most common major criterion and can contribute to an unequivocal diagnosis in 23% of cases [16].

Pulmonary manifestations

Pulmonary manifestations include spontaneous pneumothorax, and apical blebs. These findings are considered minor criteria.

Differential diagnosis

In 2004 Mizuguchi et al. [17] reported that Marfan syndrome can be caused by an interruption of TGFRB2. More recently Loeys and colleagues [18] reported that mutations in TGFBR1 cause aortic aneurisms and a marfanoid phenotype (Loeys-Dietz syndrome). While aortic dilatation is common to both Marfan syndrome and Loeys-Dietz syndrome, in the latter, ectopia lentis is rare and the patients display ocular hypertelorism (90%), cleft palate or uvula (90%) and arterial tortuousity (84%) [18]. Mutations in TGFβ receptors cause in turn increased levels of the ligand TGFβ, which is apparently responsible for some of the marfanoid features.

Many other syndromes that share features with Marfan syndrome have been reported and a partial list is provided in Table 2.

Table 2. Differential diagnosis

Skeletal manifestations
Loeys-Dietz syndrome (OMIM 190182)
Congenital contractural arachnodactyly (Beals syndrome) (OMIM 121050)
Stickler syndrome (OMIM 108300; 604841; 609508; 184840)
Klinefelter syndrome, XYY syndrome
Homocystinuria (OMIM 236200)
Marfanoid mental retardation (OMIM 309520; 248770)
Ocular findings
Stickler syndrome (OMIM 108300; 604841; 609508; 184840)
Homocystinuria (OMIM 236200) – ectopia lentis
Ehlers-Danlos syndrome, kyphoscoliosis form (type VI; OMIM 225400)
Weill-Marchesani syndrome (OMIM 277600) – ectopia lentis
Autosomal dominant ectopia lentis (OMIM 129600)
Autosomal recessive ectopia lentis with (OMIM 225200) and without (OMIM 225100) ectopic pupils
Cardiovascular features
Loeys-Dietz syndrome (OMIM 190182)
Marfan syndrome type 2 (OMIM 154705)
Mitral valve prolapse
MASS phenotype (familial mitral valve prolapse; OMIM 157700).
Erdheim cystic medial necrosis with dissection of the ascending aorta (OMIM 607086)
Familial aortic aneurysm (OMIM 132900)
Bicuspid aortic valve with dissection of the ascending aorta (OMIM 109730)

Management

The diagnosis of Marfan's syndrome requires a multidisciplinary assessment that generally includes a geneticist, an ophthalmologist, an orthopedist, and a cardiologist. Occasionally other specialists also need to be consulted.

Marfan patients are at increased risk for retinal detachment, glaucoma and cataracts. Myopia is reported in most patients and may predispose to amblyopia in early childhood. Lens dislocation may require correction either by lenses or by phacotomy and replacement of the lens. Thus, patients with the disorder should undergo comprehensive yearly assessments by an ophthalmologist experienced in this disorder.

The main orthopedic problems include kyphoscoliosis, pectus deformities, and occasionally joint and feet problems. Bracing or surgical stabilization may be required for progressive kyphoscoliosis, which must be monitored closely during growth. Some patients with pectus deformity may need surgery either for cosmetic reasons or to treat a restrictive lung disease.

Medical treatment

Beta-adrenergic receptor blockade to delay or prevent aortic aneurysm and dissection is currently regarded as the standard of care of practice for Marfan patients [19]. Beta-blockers are probably beneficial both through negative inotropic and negative chronotropic effects. For patients who are intolerant to beta-blockers, a trial of verapamil or angiotensin-converting enzyme inhibitor may be justified [20,21].

Aortic growth is slowed in response to treatment but can not be stopped. Thus, yearly measures of aortic dimensions should be monitored, and if significant dilatation is present, monitoring should be more frequent.

Surgery

When the aortic diameter reaches 5 cm elective surgery is recommended. A family history of aortic dissection less than 5 cm and an increase in aortic diameter exceeding 1 cm per year are also indications for surgery [22].

The traditional composite aortic graft surgery is associated

with risks of thromboembolism requiring lifetime warfarin anticoagulation. In recent years surgical attempts to maintain the native aortic valve showed encouraging results and is now the preferred treatment, particularly for women in the childbearing age [23,24].

Lifestyle modifications

Patients should be counseled not to engage in contact sports, competitive athletics, or isometric exercise because of increased risk of aortic dilatation and rupture. Nevertheless, whenever possible, patients should be encouraged to maintain moderate aerobic activities. This will promote skeletal, cardiovascular and psychosocial health in the long term [25].

Pregnancy

Genetic counseling should be given to prospective parents. They should be informed of the 50% risk of an affected offspring, and prenatal diagnosis, either by mutation analysis or by linkage, should be discussed. Preimplantation genetic diagnosis should also be discussed. For patients who have undergone composite graft surgery, systemic anticoagulation with warfarin is associated with increased risk of warfarin embryopathy and fetal loss. Subcutaneous low molecular weight heparin seems safer than warfarin during pregnancy since it does not cross the placenta, however it might not prevent prosthetic valve thrombosis [26,27].

Pregnancy imposes a risk of aortic enlargement and rupture. This risk is related to the size of the aortic root before pregnancy. If the aortic root measures less than 4 cm, the risk of pregnancy is low [28].

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