

Marfan Syndrome – an Overview

Introduction

Marfan Syndrome (MFS) is a dominantly inherited systemic connective tissue disorder characterized by multiple variable abnormalities of the skeletal, ocular, cardiovascular, pulmonary, skin, and nervous systems (1, 2). The skeletal manifestations give rise to the characteristic appearance of MFS patients, with tall, thin stature and long limbs and digits. However, the clinically most severe complications of MFS are the cardiovascular manifestations – particularly aortic dilation and dissection. Aortic dilation can be slowed through pharmacologic treatment, and aortic dissection can be prevented by prophylactic aortic root replacement surgery (3,4). Early diagnosis of MFS is therefore critical, to allow timely initiation of drug treatment and regular assessment of aortic dilation, as well as life-style adjustments to prevent acute complications such as pneumothorax. However, diagnosis of MFS is complicated by the variable expression and age at onset of manifestations, of which many in isolation are relatively common and not specific to MFS. Since a mutation in the gene *FBN1* can be detected in about 90% of patients with a clinical diagnosis of MFS according to the Ghent criteria (see Table 1), genetic testing can help to identify individuals who should be monitored for onset of aortic dilation. In a large series of probands, diagnosis of MFS based on clinical criteria alone missed 11% of adults and 29% of children with pathogenic *FBN1* mutations, who could be identified by genetic testing (5). Genetic testing allowed diagnosis of MFS in about half of the adults with only partially fulfilled clinical criteria. In another series, genetic testing was used to exclude MFS in 32 out of 51 presymptomatic young relatives of MFS patients with known *FBN1* mutations, obviating the need for further monitoring (6). Prevalence of MFS is estimated at 1 in 5,000. About 25% of MFS is sporadic, ie, occurs in the absence of family history (1,2).

Molecular Pathophysiology

The gene *FBN1* codes for fibrillin, which assembles into the microfibrils connecting other structural proteins that confer elasticity to connective tissue. In the eye, microfibril bundles anchor the lens (7). Fibrillin also appears to play a role in regulating bioavailability of transforming growth factor beta (TGFbeta), a key factor in tissue homeostasis (8). Loss-of-function mutations in *FBN1* are thought to cause ocular MFS symptoms such as ectopia lentis directly through disturbing microfibril assembly and to lead to other symptoms, such as skeletal and cardiovascular manifestations, indirectly through an effect on TGFbeta signaling (4,9-11). While type or location of a mutation cannot be used to definitively predict the type or severity of manifestations, some correlations between genotype and phenotype have been established. Specifically, mutations leading to synthesis of a truncated protein (nonsense or frameshift mutations) are often associated with severe skeletal manifestations; missense mutations producing a cysteine are likely to cause ectopia lentis; and mutations located in exons 24 through 32 often lead to a more severe and complete phenotype, with younger age of onset (12).

Clinical Presentation

Initial presentation of MFS is typically in childhood or adolescence and most commonly involves skeletal and/or ocular manifestations (1,2). Characteristically, MFS patients are taller than expected from their genetic background, with loose joints and long, slender limbs and digits. Other skeletal manifestations include either outward (pectus carinatum) or inward (pectus excavatum) deformation of the sternum, scoliosis, flat feet, and a highly arched palate with crowding of teeth. The most characteristic ocular manifestation is ectopia lentis (lens displacement is usually

upward), which occurs in more than half of MFS patients. Other ocular problems include severe myopia, retinal detachment, and glaucoma. The most common cardiovascular manifestation is progressive aortic dilation, which can lead to fatal aortic dissection – usually at the aortic root –, aortic rupture, and/or aortic regurgitation. Mitral valve prolapse is also common and is the cause of congestive heart failure in neonatal MFS.

Diagnosis

Since no single manifestation by itself is specific for MFS, diagnosis of MFS is based on the occurrence of characteristic manifestations in at least three different organ systems, as specified in the so-called Ghent criteria (see Table 1). In the presence of a confirmed family history of MFS or if a mutation known to be associated with MFS is detected, occurrence of characteristic manifestations in just two organ systems is sufficient for a diagnosis of MFS. Presence of a pathogenic *FBN1* mutation is not considered diagnostic by itself because MFS is clinically and not molecularly defined. If occurring in isolation, the “component” phenotypes of MFS are considered distinct “type I fibrillinopathies,” such as mitral valve prolapse syndrome, familial ectopia lentis, and the MASS (mitral valve, aorta, skeleton, and skin) phenotype (2). In general, these milder *FBN1*-related phenotypes “run true” within families, but onset of progressive aortic dilatation later in life in individual family members cannot be excluded (2,13). For these reasons, genetic testing of all patients with MFS or another type I fibrillinopathy and their first degree relatives is indicated, and regular clinical assessment of all carriers of pathogenic *FBN1* mutations, including asymptomatic individuals, is advisable. Vice versa, family members not carrying a known familial *FBN1* mutation are not at increased risk of progressive aortic dilation and do not need to undergo regular screening (6). Of note, a number of other conditions that are not or

rarely caused by *FBN1* mutations also show phenotypic overlap with MFS, such as Shprintzen-Goldberg syndrome, congenital contractural arachnodactyly, Ehlers-Danlos syndrome, homocystinuria, familial thoracic aortic aneurysm syndrome, and Loeys-Dietz syndrome (2).

Treatment

Treatment of MFS depends on the type and severity of manifestations (1-4). All patients with MFS should be regularly monitored by a cardiologist, ophthalmologist, and orthopedist with experience in treating MFS. Beta blockers are typically prescribed to reduce the pressure on the aortic wall and delay aortic dilation. If beta blockers are contraindicated, a calcium channel blocker may be chosen. Recently, the angiotensin II type 1 receptor blocker losartan, which down-regulates TGFbeta activity, was shown to prevent cardiovascular and ameliorate non-cardiovascular manifestations in the murine model of Marfan syndrome. Efficacy of losartan in humans is currently being tested in clinical trials. Prophylactic aortic root replacement, which has a much higher treatment success than emergency root replacement, is recommended if one of the following applies: the aortic diameter exceeds 5 cm (in adults); the rate of dilation is greater than 1 cm per year; moderate aortic regurgitation is present; the patient has a family history of premature aortic dissection. In addition, patients are advised to avoid contact sports and high-intensity or isometric exercise, which increase the risk of aortic dissection even at small degrees or rates of aortic dilation, as well as activities that include breathing against resistance, which can lead to pneumothorax. Antibiotic prophylaxis for dental, gastrointestinal, or genitourinary procedures is advised for patients with mitral valve prolapse or valve-sparing aortic root surgery.

Table 1: Ghent Criteria for Diagnosis of Marfan Syndrome

Minimal requirements: major criteria in 2 organ systems and minor criteria in a 3rd

Organ system	Major criteria	Minor criteria
Skeletal	At least 4 of the following manifestations: <ul style="list-style-type: none"> • Pectus carinatum • Pectus excavatum (req. surgery) • Reduced upper to lower segment ratio or arm span to height ratio of >1.05 • Wrist and thumb signs • Reduced extension at elbows (<170°) • Scoliosis of >20° • Pes planus • Protrusio acetabulae 	At least 2 manifestations listed under major criteria, or 1 listed under major criteria and 2 of the following: <ul style="list-style-type: none"> • Pectus excavatum (not requiring surgery) • Joint hypermobility • Highly arched palate with crowding of teeth • Facial appearance (dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures)
Ocular	Ectopia lentis	At least 2 of the following: <ul style="list-style-type: none"> • Abnormally flat cornea • Increased axial length of the globe • Hypoplastic iris or hypoplastic ciliary muscle, causing decreased miosis
Cardio-vascular	At least 1 of the following: <ul style="list-style-type: none"> • Dilatation of the ascending aorta involving the sinuses of Valsalva • Dissection of the ascending aorta 	At least 1 of the following: <ul style="list-style-type: none"> • Mitral valve prolapse • Unexplained dilatation of the main pulmonary artery before age 40 • Calcification of mitral annulus before age 40 • Dilatation or dissection of descending thoracic or abdominal aorta before age 50
Nervous	Lumbosacral dural ectasia	
Pulmonary		At least 1 of the following: <ul style="list-style-type: none"> • Spontaneous pneumothorax • Apical blebs
Skin and Integument		At least 1 of the following: <ul style="list-style-type: none"> • Unexplained striae atrophicae • Recurrent or incisional herniae
Genetics/ Family History	At least 1 of the following: <ul style="list-style-type: none"> • <i>FBN1</i> mutation previously associated with MFS • First degree relative with confirmed diagnosis of MFS 	

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