Review

Marfan syndrome: An eyesight of syndrome ☆

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ABSTRACT

Marfan syndrome (MFS), a relatively common autosomal dominant hereditary disorder of connective tissue with prominent manifestations in the skeletal, ocular, and cardiovascular systems, is caused by mutations in the glycoprotein gene fibrillin-1 (FBN1). Aortic root dilation and mitral valve prolapse are the main presentations among the cardiovascular malformations of MFS. The revised Ghent diagnostics nosology of Marfan syndrome is established in accordance with a combination of major and minor clinical manifestations in various organ systems and the family history. The pathogenesis of Marfan syndrome has not been fully elucidated. However, fibrillin-1 gene mutations are believed to exert a dominant negative effect. The treatment includes prophylactic β-blockers and angiotensin II-receptor blockers in order to slow down the dilation of the ascending aorta and prophylactic aortic surgery. Importantly, β-blocker therapy may reduce TGF-β activation, which has been recognized as a contributory factor in MFS. The identification of a mutation allows for early diagnosis, prognosis, genetic counseling, preventive management of carriers and reassurance for unaffected relatives. The importance of knowing in advance the location of the putative family mutation is highlighted by its straightforward application to prenatal and postnatal screening. The present article aims to provide an overview of this rare hereditary disorder.

Contents

Introduction

In 1896 Antoine Marfan (French pediatrician) first described the Marfan syndrome (MFS) in a five and half-year-old girl (Van de Velde et al., 2006). MFS (OMIM #154700) is an inherited, autosomal dominant disorder with a high degree of clinical variability that affects many parts of the body like skeletal, ocular and cardiovascular systems etc. (Haneline and Lewkovich, 2007). MFS affects males and females equally and the mutation shows no ethnic or geographical or gender bias. Flo Hyman (Olympic silver medalist in Women's Volleyball 1984), Jonathan Larson (author and composer of *Rent*), Vincent Schiavelli (an actor and spokesperson for the National Marfan Foundation), Niccolò Paganini and Robert Johnson (Musicians and composers) and former American President Abraham Lincoln manifested several key clinical features of MFS (science.jrank.org., 2010; www.marfan.org., 2010). The estimated prevalence of the disease ranges from 1 in 5000 to 1 in 10,000 live newborns (Faivre et al., 2007; Pearson et al., 2008). Myopia is the most common ocular feature and the displacement of the lens from the center of the pupil observed in approximately 60% of affected individuals. People with MFS are at increased risk for retinal detachment, glaucoma, and early cataract formation (Ahram et al., 2009). The skeletal system involvement is characterized by bone overgrowth and joint laxity. The extremities are disproportionately long for the size of the trunk (dolichostenomelia). Approximately 25% of MFS patients have cutaneous features and no craniofacial dysmorphology. The major sources of morbidity and early mortality in the MFS relate to the cardiovascular system. Cardiovascular manifestations include dilatation of the aorta at the level of the sinuses of Valsalva, a predisposition for aortic tear and rupture, mitral valve prolapse (MVP) with or without regurgitation, tricuspid valve prolapse (TVP) and enlargement of the proximal pulmonary artery (Geva et al., 1987). Pregnancy can be dangerous for women with MFS, especially if the aortic root exceeds 4.0 cm. Complications include rapid progression of aortic root enlargement and aortic dissection or rupture during pregnancy, delivery and the postpartum period (Silverman et al., 1995). In this manuscript, we are discussing the molecular pathogenesis, genetics, diagnosis as well as the current therapeutic strategy of the disease.

Genetic insight of the disease

The gene linked to the MFS disease was first identified by Francesco Ramirez at the Mount Sinai Medical Center in New York City in 1991 (Brown, 2008). The majority of cases of MFS (MFS1) are caused

by a mutation in the fibrillin-1 gene (*FBN1*) on chromosome 15 (15q21.1) and the marked phenotypic heterogeneity is observed in MFS (Ammash et al., 2008). The transforming growth factor-beta receptor-2 gene (TGFBR2) has been associated with a second type of this disorder i.e. MFS type 2 (MFS2) with typically mild or absent ocular involvement (Eliana et al., 2006; Singh et al., 2006). *FBN1* is a 230-kb gene with 65 exons that encodes the structural protein fibrillin-1 (Corson et al., 1993). Fibrillin-1 is a matrix glyco protein widely distributed in elastic and nonelastic tissues. *FBN1* mutations result in the production of abnormal fibrillin proteins and when incorporated into microfibrils along with normal fibrillin proteins result in structurally inferior connective tissues. Two-thirds of the mutations are missense mutations and the majority of these are cysteine substitutions. Nonsense mutations comprise about 10% of all reported mutations. Small insertions, deletions, or duplications represent about 13% of all reported mutations. Another 13% of the reported mutations consist of various classes of splicing errors (Robinson et al., 2006). Premature termination codons (PTCs) and in-frame mutations are the two major mutation categories in the *FBN1* gene (Collod-Beroud et al., 2003).

Approximately 75% cases of MFS have an affected parent and remaining 25% of probands have a de novo mutation. If a parent of the proband is affected, the risk to the sibs is 50% (Keane and Pyeritz, 2008). The phenomenon of anticipation has not been observed in MFS.

Molecular pathogenesis of MFS

The various manifestations of MFS are today considered to be the result of an overall abnormality in the homeostasis of the extracellular matrix, in which reduced or mutated forms of fibrillin-1 lead to alterations in the mechanical properties of tissues, increased TGF-β activity and signaling, and loss of cell–matrix interactions (El-Hamamsy and Yacoub, 2009). The abnormal homeostasis is thought to result in vascular remodeling, characterized by an exaggerated elastolysis as a result of over expression of matrix metalloproteinases (MMP-2 and MMP-9) and increased hyaluronan content that slowly degrade the elastin fibers and other components of the extracellular matrix i.e. ECM (Nataatmadja et al., 2006). Transforming growth factor beta (TGFβ) plays an important role in Marfan syndrome. Fibrillin-1 directly binds to a latent form of TGFβ and sequesters TGFβ and thus TGFβ is unable to exert its biological activity (Table 1, Fig. 1). The simplest model of Marfan syndrome suggests that reduced levels of fibrillin-1 (due to mutation and several other factors) allow TGFβ levels to rise due to inadequate sequestration and thus TGFβ shows deleterious effects on vascular smooth muscle development and the integrity of the extracellular matrix. Although it is not proven how elevated TGFβ levels are responsible for the specific pathology of the disease.

The development of several mouse models of the disease has contributed greatly to our current knowledge of the molecular pathogenesis of MFS. These models have shown that fibrillin-1 is not essential

Table 1
Summary of the Marfan syndrome (MFS).

Characteristics	Description
(1) OMIM for MFS	154700
(2) Gene	FBN1
(3) Gene location	15q21.1
(4) OMIM for FBN1 gene	134797
(5) Mutation	Missense, nonsense, insertion, deletion, duplication and splice site
(6) Molecular pathogenesis	TGFβ and FBN1 interaction
(7) Diagnostic criteria	Revised Ghent nosology
(8) Clinical diagnosis	Echocardiography, MRI, computed tomography, X-ray and ultrasound, slit lamp examination of eye
(9) Biochemical diagnosis determinants	XOD, NOS, NADPH oxidase, SOD
(10) Molecular diagnosis	XOD, NOS, NADPH oxidase, SODPCR, MDA, primary sequencing and deletion–duplication studies, DNA fingerprinting and microarray technology
(11) Therapeutics substances and therapy/ procedure	Beta blockers, angiotensin receptor "antagonists", Verapamil or other calcium channel blockers, perindopril therapy and Nuss procedure

OMIM: Online Mendelian Inheritance in Man; FBN1: *Fibrillin 1*; TGFβ: Tumor growth factor beta; XOD: Xanthine oxidase; NOS: Nitric oxidase synthetase; SOD: Superoxide dismutase; MDA: Multiple displacement amplification.

in elastogenesis (Pereira et al., 1999). They have provided insights into the regulatory role of fibrillin-1 and into the implication of increased TGF-β signaling in the development of some manifestations of the disease, such as impaired pulmonary alveolar septation or myxomatous thickening of mitral valve (Neptune et al., 2003; Ng et al., 2004). Notably, treatment of these fibrillin-deficient mice with TGF-β-neutralizing antibodies prevented or attenuated both manifestations and had a beneficial impact on the phenotype (Neptune et al., 2003; Ng et al., 2004). In an elegant mouse model of MFS, Habashi et al. showed that excessive TGF-β signaling also had a causal role in the development of aortic root aneurysms (Habashi et al., 2006), the most feared manifestation of Marfan syndrome. The treated mice exhibited reduced fragmentation of the elastic fibers and slower growth of the aortic root in comparison with the placebo group (Habashi et al., 2006). Most studies of MFS have focused on canonical TGF-β signaling, and growing evidence now shows that noncanonical signaling pathways such as those involving the mitogen activated protein kinases (MAPKs) also have an important role in aneurysm development (Holm et al., 2011). It was observed in aortas of fibrillin-1-deficient mice that TGF-β-dependent and angiotensin II type 1 receptor (AT1R)-dependent activation of ERK1 and ERK2 was involved in the pathogenesis of disease (aneurysm formation). Further evidence for their importance was obtained from the abrogation of pathological aortic root growth after treatment with a specific ERK inhibitor (Habashi et al., 2011).

Diagnosis of the disease

An early presentation of Marfan syndrome includes tall stature, ectopia lentis, scoliosis, mitral valve prolapse (MVP), aortic root dilation and aortic dissection. The diagnosis of MFS should be made in accordance with the revised Ghent diagnostic nosology which involves major and minor diagnostic findings (Loeys et al., 2010; Table 1) and is largely based on clinical manifestations from various organ systems and on the family history. Major diagnostic criteria include enlarged aorta, tear in the aorta, dislocation of the lens, family history of the syndrome, at least four skeletal problems such as flat feet or curved spine and dural ectasia (enlargement of the lining that surrounds part of the spinal cord) while minor criteria include short sightedness (myopia), unexplained stretch marks, loose joints. A tall, thin body habitus, long limbs, arachnodactyly, pectus deformities and sometimes scoliosis with a positive family history in a young individual may be suggestive of a diagnosis of MFS (Dean, 2007).

Clinical and biochemical diagnosis

Marfan syndrome is a clinical diagnosis based on family history and the observation of characteristic findings in multiple organ systems. In the presence of a family history of MFS, the diagnosis can be established for a first-degree relative of the proband in three scenarios: (i) Ectopia lentis, (ii) systemic score ≥ 7, and (iii) aortic root enlargement (Z-score ≥ 2.0 in those aging ≥20 years or ≥3.0 in those aging <20 years). In the absence of a family history of MFS, the diagnosis can be established for a proband in four scenarios: (i) Aortic root enlargement (Z-score ≥ 2.0), (ii) a pathogenic *FBN1* mutation, (iii) a systemic score ≥ 7, and (iv) Ectopia lentis and a *FBN1* mutation previously associated with aortic enlargement (Arbustini et al., 2005).

Echocardiography technique detects aortic root dilation and mitral valve prolapse. In Marfan patients, 60% have aortic root dilation, 91% have mitral valve prolapse and 23% have aortic regurgitation (Come et al., 1983). The incidence of aortic dilation and mitral prolapse in MFS has been found to be essentially equal in children and adults of the same sex (Brown et al., 1975). Transesophageal echocardiography and magnetic resonance imaging (MRI) are preferred over contrast aortography for diagnosing aortic dissection in pregnant patients with Marfan syndrome (Elkayam et al., 1995; Table 1). The use of radiation needs to be minimized, with adequate shielding for the fetus, if contrast aortography cannot be avoided (Elkayam et al., 1995). Ultrasound with higher sensitivity has demonstrated mild myocardial impairment in such patients (Kiotsekoglou et al., 2009; Table 1).

The levels of xanthine oxidase (XOD), intracellular nitric oxidase synthetase (iNOS), NAD(P)H oxidase and 8-isoprostane were higher in the Marfan group than in the control but SOD-1 and SOD-2 expressions were decreased in Marfan aortas (Yang et al., 2010; Table 1).
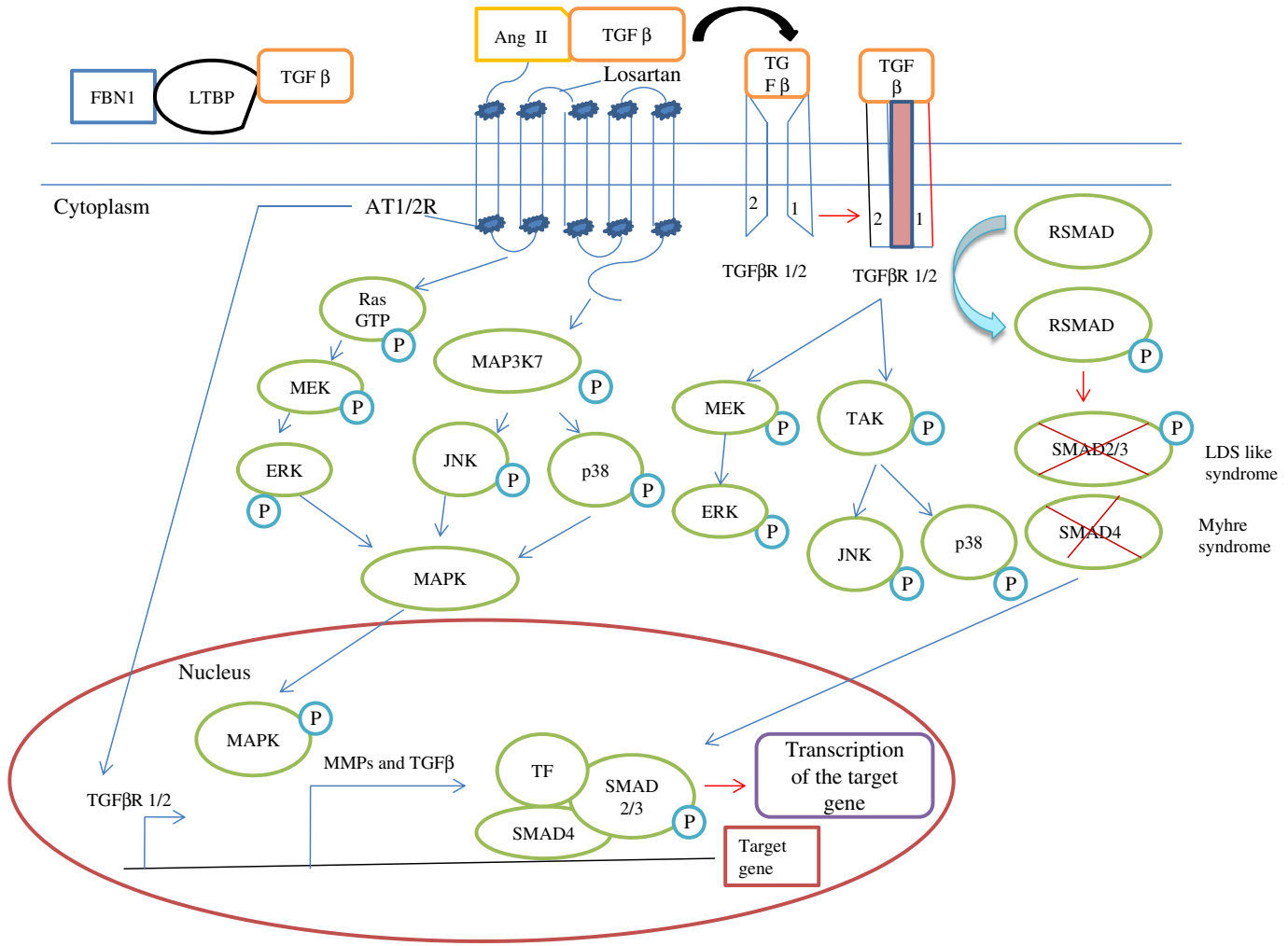
Molecular diagnosis

Molecular analysis of *FBN1* is involved in the identification of individuals with marked intrafamilial variability. Mutation analysis may be critical for identifying patients and relatives who require lifelong aortic follow-up with isolated ectopia lentis or isolated major skeletal involvement (Faivre et al., 2008).

Sequence analysis and mutation scanning

The mutation detection rate of *FBN1* mutation scanning and cDNA sequence analysis ranges from approximately 70% to 93% (Arbustini et al., 2005; Halliday et al., 2002; Korkko et al., 2002; Loeys et al., 2004; Stheneur et al., 2009) and is influenced by: (i) the accuracy of the clinical diagnosis of Marfan syndrome (i.e. individuals fulfilling the established clinical diagnostic criteria with positive family histories are much more likely to have a detectable *FBN1* mutation), (ii) type of mutation and (iii) mutation detection methodology (Stheneur et al., 2009).

Deletion/duplication analysis

The functional haploinsufficiency mechanism is involved in the causative feature of Marfan syndrome (Judge et al., 2004). This hypothesis was validated by the identification of persons with Marfan syndrome with large genomic deletions of regulatory elements that abolish transcription from the mutant allele (Matyas et al., 2007). On this basis, multiple clinical laboratories perform assays aimed at detecting large deletions if sequence analysis or mutation scanning does not detect a mutation.

Linkage analysis

Linkage analysis may be used to determine if an individual has inherited an *FBN1* allele that is associated with Marfan syndrome in family members. The markers used for MFS linkage are highly informative and are within *FBN1* and they can be used in nearly 100% of the families. Linkage testing is not available to families in which only a single member is affected. Linkage analysis should be used with great caution particularly in families exhibiting atypical phenotypes because multiple phenotypes with some clinical overlap with MFS are not caused by mutations in *FBN1* and locus heterogeneity for MFS has not been definitely excluded (Schleutermann et al., 1976).

Prenatal diagnosis

Molecular genetic testing

Prenatal diagnosis for pregnancies at increased risk for MFS is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks gestation or chorionic villus sampling (CVS) at approximately 10 to 12 weeks gestation. The disease-causing allele of an affected family member must be identified or linkage established in the family before prenatal testing. Linkage analysis should be used with caution unless *FBN1* marker alleles can be shown to co-segregate with disease in a large family.

Fig. 1. Molecular pathogenesis and therapeutics of Marfan syndrome (MFS). At the cell surface, Fibrillin-1 directly binds a latent form of TGFβ binding protein (LTBP). TGF-β and angiotensin II (via Ang II receptor type 1, AT1R) activated Ras can induce ERK MAP signaling. JNK and p38 MAPK signaling are activated by various MAPK kinase kinases in response to varied stimuli. Whereas MAP/ERK kinases (MEK1) and TGF-β-activated kinases (TAK1) can activate ERK, JNK and p38 signaling pathways and thus relay the signal into the nucleus causing the transcription of target genes (non-canonical TGF β pathway). TGFβ downstream signaling involves SMAD 2, 3 and 4 (canonical TGF β pathway). MAPK: mitogen-activated protein kinases; TGF-β: transforming growth factor beta; JNK: Janus kinase.

Ultrasound examination

It is insensitive in detecting manifestations of Marfan syndrome in the first two trimesters (Burke and Pyeritz, 1998).

Preimplantation genetic diagnosis (PGD)

It may be available for families in which the disease-causing mutation has been identified. Despite the significant advantage provided by PGD there are still technical limitations. There is a need for a technique that would be able to amplify the single-cell DNA with a high fidelity that suits the diagnosis of MFS by standard PCR technique. Multiple displacement amplification (MDA) is a technique used in the amplification of very low DNA quantities in clinical samples (Lledo et al., 2006; Table 1). For molecular diagnosis, future improvements include the use of quantitative PCR, DNA fingerprinting and microarray technology (Basille et al., 2009; Table 1).

Management and therapeutic approach

Management is most effectively accomplished through the coordinated input of a multidisciplinary team including a geneticist, cardiologist, ophthalmologist, orthopedist and a cardiothoracic specialist.

Eye management

Mostly, eye problems can be adequately controlled with eyeglasses alone. Lens dislocation can require surgical aphakia (removal of lens) if the lens is freely mobile or the margin of the lens obstructs vision. An artificial lens can be implanted once growth is complete. While this procedure is currently considered quite safe when performed in specialized centers, major complications, including retinal detachment, can occur. Careful and aggressive refraction and visual correction is mandatory in young children at risk for amblyopia.

Skeletal management

Bone overgrowth and ligamentous laxity can lead to severe problems and should be managed by an orthopedist; surgical stabilization of the spine may be required. Pectus excavatum can be severe and surgical intervention is medically indicated. Protusio acetabulae is associated with pain or functional limitations. However, surgical intervention is rarely indicated. Pes planus is often associated with inward rotation at the ankle, leg fatigue and muscle cramps. Dental crowding requires orthodontia or use of a palatal expander. Use of hormone supplementation to limit adult height is rarely requested or considered. Complications include the psychosocial burden of accelerated puberty and perhaps the undesirable consequences of the increased blood pressure associated with puberty on progression of aortic dilatation. This treatment should only be considered when an extreme height is anticipated. MFS-specific growth curves now allow accurate prediction of adult height (Erkula et al., 2002).

Cardiovascular management

Cardiovascular manifestations should be managed by a cardiologist who is familiar with MFS. Surgical repair of the aorta is done in the following conditions: (i) the maximal measurement approaches 5.0 cm in adults or older children, (ii) the rate of increase of the aortic diameter approaches 1.0 cm per year or (iii) there is progressive aortic regurgitation. More aggressive therapy is indicated in individuals with a family history of early aortic dissection. Many individuals receive a valve-sparing procedure that precludes the need for chronic anticoagulation. Most often the mitral valve can be repaired rather than replaced.

Pregnancy management

Pregnant women with Marfan syndrome have the potential to present acute aortic dissection, especially under conditions of aortic root dilation (Sakaguchi et al., 2005) and fetal death (Cañadas et al., 2010) or in cases of inheritance of this disease by the child (Goland et al., 2009). Complications such as rapid aortic dilation and aortic dissection may occur at any time during pregnancy or even postpartum but most often in the third trimester (Keskin et al., 2002). Cesarean section is preferred in women with aortic dilation (Stanley et al., 2003). An aortic root diameter of less than 40 mm would result in favorable maternal and fetal outcomes (Rossiter et al., 1995). High-intensity static exercise should be discouraged although low–moderate intensity dynamic exercise may be beneficial. The fetus has a 50% chance of acquiring the disease (Ryan-Krause, 2002). Cardiopulmonary bypass during pregnancy is associated with maternal mortality of 3% and fetal mortality of 20% (Pomini et al., 1996).

Others

Dural ectasia is usually asymptomatic and no effective therapies for symptomatic dural ectasia currently exist. Hernias tend to recur after surgical intervention. Pneumothorax can be a recurrent problem. Optimal management requires chemical or surgical pleurodesis or surgical removal of pulmonary blebs.

The goal of treatment is to slow the progression of aortic dilation and damage to heart valves by eliminating arrythmias and minimizing the heart rate and blood pressure (Dietz, 1993). Beta blockers, like atenolol, have been used to control arrythmias and slow the heart rate (Tahernia, 1993; Table 1) while angiotensin converting enzyme (ACE) inhibitors and angiotensin (Ang) II receptor antagonist or blockers (like losartan) minimize blood pressure without slowing the heart rate (Brooke et al., 2008; Table 1). All of the physiological effects of angiotensin II (including stimulation of release of aldosterone) are antagonized in the presence of losartan. Reduction in blood pressure occurs independent of the status of the renin-angiotensin system. As a result of losartan dosing, plasma renin activity increases due to removal of the angiotensin II feedback. Losartan is involved in the transcription of the target gene by the combined activity of different cell signaling pathways (like MAPK, Ras GTP, etc.) (Fig. 1). Now a days, losartan is successfully used in the treatment of patients affected with MFS (Habashi et al., 2011; Matt et al., 2008; Ramirez and Dietz, 2007). The use of ACE inhibitors may be more beneficial than beta-blockers (Yetman et al., 2005). The aortic root dilation and fibrillin-1 abnormalities are caused by excessive TGF-β signaling and TGF-β antagonists, including angiotensin II-receptor blockers, significantly slow down the progression of aortic root dilation or prevent certain manifestations of Marfan syndrome, including aortic aneurysm (Judge and Dietz, 2008). Perindopril therapy reduces arterial stiffness, central and peripheral pulse wave velocities, aortic root diameters (in both end-systole and end-diastole) and TGF-β in MFS patients (Ahimastos et al., 2007; Table 1). Verapamil or other calcium channel blockers (Table 1) have been suggested if beta-blockers cannot be used (individuals with asthma) or are not tolerated (prolonged lethargy and depression). The Nuss procedure (Table 1) is now being offered to people with MFS to correct 'sunken chest' or pectus excavatum.

Conclusion

Marfan syndrome is a rare hereditary connective tissue disorder affecting many parts of the body. It is associated with high morbidity and mortality in untreated patients. Establishment of a diagnosis of Marfan syndrome is based on the revised Ghent nosology, which involves comprehensive evaluation of major and minor systemic manifestations. Diagnosis remains essentially clinical, although genetic testing can be useful in selected cases. The pathogenesis of Marfan syndrome has not been fully elucidated but fibrillin-1 gene mutations are believed to exert a dominant negative effect through excessive TGF-β signaling pathways. Cardiovascular malformations, chiefly aortic root dilation and mitral valve prolapse, are the most life-threatening symptom of Marfan syndrome, since these patients are at risk of acute aortic dissection. Regular cardiovascular, ocular and skeletal surveillance by means of echocardiography, slit lamp examination of the eye, and magnetic resonance is recommended upon diagnosis or after the operation. Advances in the understanding of the genetic and molecular basis of the disease have challenged our traditional definition of the disease as a structural connective-tissue disorder.

Conflict of interests

There is no conflict of interest.

Authors' contributions

Ashok Kumar is the first author and is responsible for the conception and designing of the manuscript. Contributing author Sarita Agarwal has made substantial contributions to the design of the manuscript and the acquisition.

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