"Marfan Syndrome: A Comprehensive Guide to Pathogenesis, Diagnosis, Treatment and Medical Management"

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Abstract

A varied autosomal dominant connective tissue disorder affecting various organ systems is called Marfan syndrome (MFS). Transformational growth factor-β (TGF-β) dysregulation is caused by causative mutations in the fibrillin-1 protein. A systematic evaluation that combines clinical and genetic factors can be used to diagnose MFS. Due of the wide range of musculoskeletal symptoms associated with the illness, patients may initially see orthopedic surgeons. Spine deformity, acetabular protrusion, limb length deformity, joint laxity, and foot pathology are common musculoskeletal symptoms of MFS. Major cardiac and ocular problems are examples of non-musculoskeletal symptoms.Routine cardiovascular imaging and β-adrenergic receptor blocker medication are staples of normal medical therapy. The latter is intended to slow down the rate of aortic development. Prophylactic surgical aortic replacement is carried out when aortic dilatation reaches a threshold linked to an increased risk of dissection. Prophylactic aortic surgery and beta-blockers are part of the usual treatment, which aims to prevent ascending aortic dilatation. The average life expectancy in Marfan syndrome has increased significantly, surpassing 72 years, thanks to the effectiveness of modern medicinal and surgical treatments for aortic illness. The life expectancy of individuals with MFS has increased dramatically with current clinical management; nonetheless, there is still no known cure and fatal complications can still occur, highlighting the need for novel treatment approaches. The goal of this review is to give a general overview of this condition.

Introduction

The most notable characteristics of Marfan syndrome (MFS), an autosomal dominant condition that is very common, are its long and slender limbs and fingers, displacement of the superior lens, and potentially deadly cardiovascular problems. It is a varied connective tissue autosomal dominant condition with cardinal symptoms affecting the skeleton, eyes, and cardiovascular system. Approximately 1 in 9800 is the minimum birth occurrence.(1)

Male and female incidence of the disease is equal because there is no sex bias for it.(2)The primary cause of death is progressive aortic dilatation, which is typically maximal at the sinus of Valsalva and is linked to aortic valve incompetence. However, there may also be significant morbidity from lens dislocation, myopia, and arthritis linked to chronic joint laxity, as well as from mitral valve prolapse with incompetence. The diagnosis is frequently made in young people with long limbs, a tall, slender body type,pectus abnormalities, scoliosis, and arachnodactyly. Suspicion may be raised by further observations made in the clinic, such as a high arched palate with dental crowding, skin striae distensae, recurrent hernia, or recurrent pneumothorax. Although a family history may be useful, new mutations account for about 27% of instances.(1)Numerous studies conducted separately by different researchers worldwide have revealed that the fibrillin-1 (FBN1) gene is the most prevalent etiological element for the etiology of the disease.(3) It is located on chromosome 15q21.1 and codes for the glycoprotein FBN1, which is the main building block of the extracellular matrix-containing microfibrils (4). Professor Antoine-Bernard Marfan has been named MFS. A girl, aged 5.5, was described by Professor Marfan in the Bulletin of the Medical Society of Paris in 1896. The girl had long, thin fingers and other skeletal anomalies.(5).In MFS, cardiovascular symptoms are the primary causes of both death and morbidity. An essential component of patient therapy is the quick and accurate diagnosis of MFS in order to reduce the severity of these consequences. According to the updated Ghent nosology, molecular validation of pathogenic mutations in FBN1 can be used in addition to the specific clinical criteria used to diagnose MFS.

Pathogenesis

Initially, it was believed that mutations in FBN1 produced anomalies in the structure and function of microfibrils in the extracellular matrix, ultimately leading to a loss of integrity in the connective tissue and the development of MFS.(6)(7)(8) Microfibrils play a significant role in the process of elastogenesis and are more abundant outside the inner, amorphous core of elastin than they are within. They comprise elastic fibers' fibrillar component.(9)(10)(11)

The aortic wall's elasticity is derived from concentric laminae formed by elastin-associated microfibrils in the tunica media of the aorta, which divide smooth muscle cell layers. By connecting the subendothelial basement membrane and smooth muscle cells with the elastic laminae, they also contribute significantly to the mechanical stability of the aorta.(12) The arginine-glycine-aspartate amino acid sequences in fibrillin 1 interact with alpha-V beta-integrin 3 to adhere to and fix smooth muscle cells and coordinate elastic and contractile forces.(13)(14) The migration, proliferation, and survival of smooth muscle cells are all regulated by internegrin alpha V beta 3.(15) FBN1 mutations make fibrillin1 more vulnerable to proteolysis, which causes micro fibril fragmentation and the disarray of elastic fibers in the tunica medium of the aorta, or medial degeneration, a histological indicator of MFS.(16) These changes that occur as a result of this degeneration encourage aortic dilatation and dissection by increasing aortic stiffness and decreasing the elasticity and distensibility of the aortic wall. Diffuse calcification of the tunica media ensues after this, as elastic fibers that have lost their microfibril network are more vulnerable to calcium deposition.

Smooth muscle cells' capacity to release substances like osteoprotegerin and matrix GLA protein, which offer active protection against local calcification, is also diminished by the weaker contact between fibrillin-1 and the latter.(17) Marfan's syndrome may not be caused by a gene mutation, and individuals who do have a gene mutation may not experience the disease's clinical symptoms. The idea that fibrillin mutations affect the development of Marfan's syndrome is supported by current hypotheses. However, fibrillin-1 mutations have only been discovered in 28%–66% of Marfan syndrome cases.(18)(19) Furthermore, people with familial aortic aneurysms, mitral valve prolapse, or Marfan-like skeletal deformities including scoliosis or pectus excavatum have also been discovered to have fibrillin-1 mutations.(20) They have also been linked to a broad spectrum of fibrillinopathies, a group of connective tissue disorders that range in severity from mild phenotypes like isolated ectopia lentis to severe conditions like neonatal Marfan's syndrome, which usually results in death within the first two years of life.(21) Normally, fibrillin aggregates to create microfibrils, which give connective tissues their strength and suppleness. Fibrillin is rendered inactive by the changed gene's expression.The characteristic findings of ligamentous laxity, joint subluxation, dural ectasia, lens dislocation, and weakened artery walls causing aortic dilatation result from the impaired mechanical integrity of tissues. The extracellular matrix's growth factor availability is enhanced by inactivated fibrillin. It is believed that elevated cellular proliferation and consequent higher longitudinal bone development are caused by increased transforming growth factor β (TGF-β) bioavailability.(22)(23) The distinctively long and narrow characteristics of the Marfanoid habitus are the outcome of this growth factor regulation.(24)

Diagnosis

Early diagnosis is critical for MFS because the disease's clinical signs are progressing and sometimes fatal.(25) The disease's high percentage of spontaneous mutations, age-dependent clinical manifestations, significant interfamilial and interfamilial phenotypic variability, and resemblance in presentation to several other connective tissue diseases make diagnosis challenging in many cases.(26)(27) Tall height, ectopia lentis, scoliosis, mitral valve prolapse, aortic root dilatation, and aortic dissection are among the early symptoms of Marfan's syndrome. The Ghent nosology, a revised set of diagnostic criteria that includes both major and minor diagnostic features, should be used for diagnosing Marfan's syndrome (chart 1)(28)

and is mostly determined by the family history as well as clinical signs from different organ systems. When a young person has a positive family history and tall, slender build, long limbs, arachnodactyly, pectus deformities, and occasionally scoliosis, these characteristics may point to a diagnosis of Marfan's syndrome.(29)

MAJOR CRITERIA	MINOR CRITERIA
1.Enlarged aorta 2.Tear in the aorta 3. Dislocation of the lens 4. Family history of the syndrome	Short sightedness (myopia) Unexplained stretch marks Loose joints

Chart 1. Major and minor diagnostic findings relating to marfans syndrome

MFS is a multisystem condition that can cause symptoms in the respiratory, central nervous, pulmonary, skeletal, ocular, cardiovascular, musculoskeletal, skin, integument, and dura systems. According to the previous Ghent criteria, a minimum of two main organ systems and a slight involvement of a third organ system were needed for the diagnosis of MFS.(30)

1.Skeletal system

The most noticeable skeletal characteristic is arachnodactyly, an excessive growth of the arms and legs that causes an arm span greater than 1.05 times the height or, in adults, a decreased upper to lower segment ratio, and disproportionate overgrowth of the long bones that results in anterior chest deformity (pectus carinatum) or posterior chest deformity (pectus excavatum). Laxity or hypermobility of the joints are common symptoms of MFS. The wrist and thumb sign is caused by arachnodactyly in conjunction with loose joints. Protrusio acetabuli, pes planus, and thoracolumbar scoliosis are additional skeletal forms that can cause pain and functional restrictions. In addition, a high arched palate, dental crowding, malar flattening, micrognathia or retrognathia, a long, narrow skull (dolichocephaly), and downward-slanting palpebral fissures are commonly observed.(31)

2.Ocular system

Ectopia lentis, which affects about 60% of MFS patients, is a significant characteristic of the condition.(32) Additional characteristics of the eyes include a hypoplastic iris, retinal detachment, flat cornea, myopia, increased axial length of the globe, hypoplasia of the ciliary muscles, and a propensity for cataracts or glaucoma.(33) It's interesting to note that ectopia lentis is more common in people who have a cysteine substitution (DN mutation).(34)

3.Cardiovascular system

The most serious clinical symptom of MFS is aortic dissection, which affects around 80% of patients. It is typically preceded by aortic root dilatation. (15)(36) An aortic root diameter with a Z-score greater than 2 indicates aortic root dilatation.(37) MFS most frequently affects the atrioventricular valves, particularly the mitral valves, resulting in valve thickness, prolapse, and varying degrees of regurgitation. Prolapse of the mitral valve is more prevalent in younger women.In up to 80% of MFS patients, there is annular degeneration and dilatation. But only 25% experience a mitral valve prolapse.(38)

4.Musculoskeletal system

During childhood, skeletal anomalies may begin to develop and worsen. About 60% of Marfan patients have scoliosis, which can worsen during development spurts and cause severe deformity, discomfort, and restricted ventilatory deficit.(39) Compared to the general population, back discomfort in people with scoliosis is three times more common.(40)Scoliosis can occasionally worsen in adulthood, particularly if the angle of curvature is 4401. There is conflicting data to support the claim that patients with dural ectasia have more back discomfort. According to CT and MRI scans, dural ectasia is found in 69% and 95% of Marfan patients, respectively.(41)

5.Respiratory system

About two thirds of Marfan's syndrome patients have pectus excavatum, which, in severe cases, can be linked to a restrictive ventilatory abnormality.(42) Although it can make cardiac surgery more challenging, people typically ask for repair for aesthetic reasons. Following pectus excavatum repair, patients with Marfan's syndrome are more prone to experience delayed wound healing.(43) Since recurrence is typical in this age group, surgical correction in youngsters should be avoided.(44)

6.Central nervous system

In certain case reports, dural ectasia has been linked to intracranial hypotension-associated headache, and it may lessen the efficacy of epidural anesthesia(45)(46). Anterior sacral meningocele can cause diagnostic uncertainty when it presents as an abdominal or pelvic mass. It has been reported infrequently as a consequence of Marfan syndrome(47). In patients with Marfan syndrome, cerebral hemorrhage and other neurovascular problems are rare; however, intracranial aneurysms may be more common in those with Loeys-Dietz syndrome.(48)

7.Pulmonary system

A restrictive pattern of lung illness can result from pectus excavatum and progressive thoracolumbar scoliosis.24% of MFS patients experience spontaneous pneumothorax, which can be predisposed to by emphysema with or without distinct bullae or blebs.(49)

8.Skin, integument, and dura

Unlike individuals with other connective tissue illnesses like Ehlers-Danlos syndrome, MFS sufferers have normal skin elasticity and texture. The majority of MFS patients—two thirds—present with striae atrophicae.Inguinal hernia, which can develop in adolescence or occur at birth, is another prevalent characteristic. In 63–92% of the patients, there is ectasia of the dura, which is an expansion of the spinal canal, the dural sac, or the root sleeves.(50)Dural ectasia can cause lumbar back pain, however it is mostly asymptomatic.

Treatment

Medical

Beta-blockade is the standard medical treatment for MFS patients to prevent aortic problems.(51) Beta-blockers are thought to have positive effects on survival by lowering heart rate and left ventricular ejection fraction, which lessen hemodynamic stress on the aortic wall; increasing aortic stiffness, which leads to aortic root dilatation; and lowering the risk of aortic dissection and other cardiovascular complications, such as aortic regurgitation and the need for surgery.(52) For people older than five, the beta-blocker should be titrated to target a heart rate of less than 100 bpm following submaximal exercise.

All MFS patients, including children and those with an aortic root diameter less than 4 cm, should be taken these medications. Angiotensin II type 1 receptor blocker losartan has been shown in experiments using mice models of MFS to be able to stop the progression of aortic dilatation.Pilot research results on children with severe MFS were similarly encouraging.First of allIts antihypertensive properties and capacity to lower plasma TGF-levels, inhibit TGF-responsive gene transcription, and lower intracellular mediators of the TGF-signaling cascade, like Smad2, appear to be the cause of its benefits. Losartan also has no effect on the angiotensin II type 2 receptor, which, in contrast to the type 1 receptor, possesses anti-inflammatory and antiproliferative properties that are advantageous for maintaining aortic wall homeostasis.(53)According to a recent meta-analysis, there was no discernible difference between losartan and atenolol's impact on the rates of dilatation of the ascending aorta and aortic root, as well as on aortic complications. Neither drug was determined to be superior to the other.(54) It is recommended that patients with MFS refrain from smoking and undergo regular blood pressure checks, ensuring that their readings stay below 120/80 mmHg.(55) They shouldn't participate in sports that need a lot of physical effort or that could result in serious physical contact.However, if an athlete has any of the following conditions, it is reasonable for them to compete in low and moderate static/low dynamic sports: moderate to severe mitral regurgitation, left ventricular systolic dysfunction (ejection fraction <40%),

aortic root dilatation (Z-score>2, aortic diameter >40 mm, or >2 standard deviations from the mean relative to BSA in children or adolescents <15 years old), or a family history of aortic dissection at an aortic diameter <50 mm.(56)

Surgical

When MFS is diagnosed with type A aortic dissection, emergency aortic surgery is recommended, with a 20% operational mortality rate and a 50–70% 10-year survival rate. However, individuals receiving elective surgery had a higher survival rate than those undergoing urgent surgery, approaching that of the general population, and the risk of death linked with prophylactic aortic surgery is only 1-2%. These findings emphasize how crucial preventive aortic surgery is for individuals who have aortic root dilatation.(57)Bentall and Bono were the first to do prophylactic aortic surgery for MFS patients in 1968.89It involves reimplantation of the coronary arteries in the vascular graft and replacement of the aortic root, aortic valve, and ascending aorta with a mechanical composite graft (combined vascular and valve). There is ample evidence to support the procedure's long-term durability, repeatability, and safety.(58) Thoracic endovascular aortic repair (TEVAR) provides a less invasive option for MFS patients with thoracic aorta illness, even though conventional surgery is still the preferred course of treatment. Nevertheless, the European Position Statement states thatExcept as a stand-in operation or a bridge to definitive open surgical therapy, or after previous aortic surgery when the graft can be put over the previously placed prosthesis, TEVAR is not advised as first-line therapy in patients with connective tissue disease.(59) According to the most recent European guidelines for the diagnosis and management of aortic disorders, surgery should be chosen over TEVAR in cases of MFS, with the exception of urgent circumstances when it is necessary to provide immediate stabilization while awaiting more extensive surgical treatment.(60)

1.Surgical treatment cardiovascular involvement

Replacing the ascending aorta is the most crucial way to avoid potentially deadly consequences like aortic dissection and rupture. Prophylactic surgery is advised for ascending and descending aortic aneurysms with an aortic diameter of 50 mm. However, in patients with a family history of early dissection, rapid aortic dilatation (>2 mm/year), substantial aortic or mitral valve regurgitations, or a desire for pregnancy, the threshold diameter for the aortic root diameter is 45 mm.(61) The Bentall method, which reattaches the coronary arteries to a graft after replacing the entire aortic root, was the accepted surgical procedure for a few decades. Valve-sparing procedures have been introduced as a result of the procedure's requirement for lifelong anticoagulation.(62)

2.Endovascular treatment

For individuals without myasthenia gravis, endovascular stent graft therapy is a minimally invasive surgical procedure that effectively treats type B aortic dissections and descending aortic aneurysms. Regretfully, there is currently a dearth of conclusive data about stenting outcomes in MFS patients. The rate of periprocedural death is modest (1.9%). On the other hand, periprocedural endoleaks were twice as common (21.6%) in MFS patients as in non-MFS patients, and a significant proportion of re-interventions or surgical conversions was required, with a 12% follow-up death rate.(63)

3.Medical treatment cardiovascular involvement

3.1 B-blockers

The current standard of care for patients with MFS is to use β-blockers to prevent or delay the advancement of aortic dilatation and aortic dissection. This therapy's method of action is predicated on releasing tension in the proximal aorta. Reductions in inotropy, chronotropy, mean blood pressure, and aortic wall stress are achieved via elastin and collagen cross-linking, which also improves aorta stability.(64)Diverse investigations yielded contradictory findings about the impact of β-blockers on cardiovascular outcomes.(65)Shores et al. demonstrated in 1994 that, throughout a 10-year follow-up period, the group receiving βblocker treatment had a considerably lower proportion of aortic

dilatation than the placebo group ($p < 0.001$).(66)A 2007 meta-analysis by Gersony et al. claimedHard clinical cardiovascular endpoints are not well demonstrated by the usage of β-blockers in MFS patients. The differing age groups, the lack of information about the severity of aortic disease in patients taking β-blockers, and the different technique (combining randomized and nonrandomized data) were some of the shortcomings of the meta-analysis that the authors identified.(67)

3.2 Losartan

Angiotensin II type 1 receptor antagonist losartan lowers wall stress and arterial pressure. Losartan has been demonstrated to reduce TGF-β release in an MFS mice model, which almost entirely prevents aortic dilatation and restores normalcy to histological alterations in the aortic wall's elastic fibers.(68)Eight randomized clinical trials were initiated to show losartan's efficacy in MFS patients after this research on mice. There are now five published studies. In a short, randomized, open-label pilot research, Chiu et al. demonstrated that losartan with β-blockers lowers the aortic root dilatation rate compared to β-blockers alone ($n = 13$; 0.10 vs. 0.89 mm per year; $P = 0.02$).(69)

Current Medical Management

The goal of medical care for MFS patients is to slow down the rate of expansion of the aorta in order to avoid or postpone the necessity for life-threatening complications and surgery. Currently, ARBs and/or β-blockers are used as the first-line medical treatments for MFS. Numerous investigations were conducted to evaluate the impact of both medications, either in direct comparison or through protocols that contrasted the combination with β-blockers alone. Both medications have similar effects overall, and some research indicates that taking them both at once may be helpful.(70) (71)The dosage of the medications is determined individually for each chemical, taking symptoms, blood pressure, and heart rate (for β-blockers) into consideration. Titrating beta-blocker dosage to maximum effect is recommended, usually to a resting heart rate of less than 60 bpm if blood pressure permits.(72)

1.β-adrenergic Receptor Blockers

Because β-blockers can lower hemodynamic stress in the proximal aorta, it makes sense to use them to slow down the formation of aortic roots and prevent aortic dissection in patients with MFS. Nowadays, atenolol, metoprolol, and bisoprolol are used to treat adult patients with MFS, whereas the β-blocker atenolol is more frequently used to treat young patients. This approach to treatment dates back to research conducted in the 1970s, which demonstrated that lowering blood pressure alone was not as effective at preventing the development of aortic dissection as lowering the maximal acceleration rate of aortic pressure increase (dP/dt).(73)

2.Calcium Channel Blockers

Several research have looked into β-blockade treatment possibilities for MFS patients. The effects of calcium channel blockers (CCBs), another family of antihypertensive medicines, were assessed for the treatment of cardiovascular symptoms in patients with MFS, taking into account the hemodynamic effects of β-blocker medication. At first, a tiny clinical investigation revealed that CCBs and β-blockers had comparable therapeutic benefits.(74)Recent studies using MFS mice models, however, refuted these conclusions and showed concerning side effects of CCB treatment. Rats administered CCBs showed higher incidence of aortic aneurysm formation, rupture, and early mortality.(75) These results were also noted in a retrospective study of clinical trials evaluating the impact of CCBs versus β-blocker medication in MFS patients. Notably, acute aortic dissection and aortic surgery were more common in MFS patients treated with CCB.(76)All things considered, there is insufficient proof that CCBs are effective in treating Marfan illness, and given their possible negative side effects, patients with MFS should refrain from using CCBs.

3.Renin Inhibitor

Using aortic measures as the major readout, a small prospective randomized clinical study was conducted to assess the possible additional benefit of combining renin inhibition with regular β-blocker medication.(77) Compared to patients receiving atenolol alone, patients with MFS receiving the renin inhibitor aliskiren in addition to atenolol did not exhibit any improvement in aortic diameter or central aortic stiffness. The results of this study suggest that renin is probably not a good target for the therapy of MFS, notwithstanding the small number of patients examined.

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