Review Article

Marfan Syndrome: A Clinical Update

Abstract

Marfan syndrome is a connective tissue disorder that can affect many organ systems. Affected patients present with orthopaedic manifestations of the syndrome during all phases of life. Pain caused by musculoskeletal abnormalities often requires definitive orthopaedic treatment. Orthopaedic surgeons must understand the phenotypes of Marfan syndrome so they can recognize when screening is warranted and can appropriately address the skeletal manifestations. Through medical advancements, patients with Marfan syndrome are living longer and more active lives. Knowledge of the latest diagnostic criteria for the disorder, as well as of advances in understanding the skeletal phenotype, clinical trials of medication therapy, and lifestyle considerations is important for orthopaedic surgeons who treat these patients because these clinicians often are the first to suspect Marfan syndrome and recommend screening.

Marfan syndrome (MFS) is an autosomal dominant disorder best known for its associated cardiovascular abnormalities. It is now understood to affect many other systems, including the ophthalmologic and pulmonary systems. Musculoskeletal symptoms include generalized ligamentous laxity, scoliosis, chest deformity, protrusio acetabuli, foot deformities, hypermobility, dural ectasia, and low bone mineral density.

The protein encoding fibrillin-1, known as the FBN1 gene, is located on chromosome 15.1 Fibrillin-1 is the main component of elastic matrix microfibrils, which have a role in the connective tissue of the cardiovascular and musculoskeletal systems. Although cardiovascular manifestations are the main cause of death in patients with MFS, medical therapies combined with early surgical management, serial cardiac imaging, refined exercise participa-

4. The initial suspicion of the role of transforming growth factor-beta (TGF-β) in MFS is now confirmed.3 Studies of mice showed that fibrillin-1 deficiency leads to an increase in TGF-β, and the excessive signaling and activation of TGF-β are theorized to cause the various manifestations of MFS.4,5

Advanced medical and surgical therapies for aortic dilatation allow patients with MFS to live longer. Life expectancy has increased from 47 years to 75 years.6 Furthermore, aortic measurement surveillance through echocardiography has allowed cardiologists to better tailor treatment with angiotensin-receptor blockers and β-blockers. Surgical interventions continue to evolve and include valve-sparing and composite graft replacement techniques. Cardiac surgeons are seeing musculoskeletal manifestations of the disease,
which require the attention of orthopaedic surgeons.

Diagnosis

The diagnosis for MFS has evolved recently, because various clinical expressions of the disease have been identified. The main clinical attributes of MFS are long bone overgrowth, dislocated lenses of the eye, and aortic root aneurysm. In 1991, Dietz et al reported that a mutation of the FBN1 gene resulted in MFS, and in 1996, the Ghent nosology criteria were established. These diagnostic criteria stress the importance of a positive genetic finding and help differentiate MFS from other disorders with similar symptoms. More than a decade later, an expert panel reconvened in Brussels, Belgium, to modify the nosology to better identify MFS and related disorders.

In the revised nosology, several major changes were made to the diagnostic criteria for MFS. More diagnostic weight is given to the presence of aortic root enlargement and ectopia lentis, the cardinal features of MFS (Table 1). Aortic root measurements have been standardized through the use of the Z-score, which accounts for body surface area, as well as the aortic root measurement (ie, aortic root diameter measurement at the sinuses of Valsalva), seen on echocardiography. Genetic testing is emphasized, particularly testing for a mutation of FBN1, which has a detection rate of 97%. Clinical testing to identify possible alternative diagnoses that overlap with MFS is recommended, and certain MFS clinical findings have been deemed less important or have been removed from the diagnostic evaluation. Counseling and follow-up recommendations for those diagnosed with MFS are also provided in the revised nosology.

The revised classification includes a systemic scoring system that emphasizes various clinical features of the disease (Table 2). MFS can be diagnosed or excluded using this scoring system in conjunction with the presence or absence of a family history of the disorder. The scoring system also accounts for the fact that phenotypic features evolve over time and may not all be present at birth or in young children, enabling providers to identify patients who warrant follow-up.

Radiography, family history, and genetic testing are used in the diagnosis of MFS. It is important for orthopaedic surgeons to recognize the signs of MFS; however, a
diagnosis should come from a geneticist. Genetic specialists are aware of the indications for and implications of genetic testing and of the differential diagnoses. The cost of testing typically is covered by insurance. Prompt diagnosis and treatment are essential to optimize outcomes.

**Clinical Manifestations**

**Cardiovascular**

The cardiovascular manifestations of MFS are well established. The main cause of death in patients with MFS is aortic root dissection. Other manifestations include mitral valve prolapse, pulmonary artery enlargement, and left ventricular dilatation.

Serial clinical examinations and echocardiography help the clinician to identify patients at risk of increased left ventricular dilatation. Management of cardiovascular manifestations typically begins with β-blocker medication, although several alternative medications have been investigated. In a recent randomized, double-blind trial, patients aged 6 months to 25 years were studied to determine whether angiotensin II type 1 receptor blockade was as effective as β-blockers, the current standard of care. Research suggests that angiotensin II type 1 receptor blockade has attenuated TGF-β signaling in other diseases by lowering the expression of the ligand,5,13 receptors,14 or activators.15 This study found that both agents were effective, with no substantial difference in aortic root dilatation (based on the Z-score) between the β-blocker group and the angiotensin II type 1 receptor blockade group.12

**Ocular**

Annual ophthalmic examinations are encouraged for patients with MFS. Superiorly dislocated lenses, myopia, glaucoma, cataracts, and retinal detachment are some of the ocular manifestations associated with MFS. Ocular conditions may be the initial presenting symptoms in patients in whom cardiovascular symptoms have not yet developed and should prompt a more advanced diagnostic workup.

**Musculoskeletal**

The main orthopaedic feature of MFS is overgrowth of the long bones.16 This overgrowth produces a tall stature and may affect the ribs, displacing the sternum anteriorly or posteriorly (pectus carinatum or pectus excavatum, respectively; Figure 1). Abnormally long fingers, also known as arachnodactyly, frequently are seen. A positive wrist sign occurs when the contralateral thumb overlaps the entire nail of the little finger when grasping the opposite wrist. A positive thumb sign occurs when the entire distal phalanx of the clenched thumb protrudes beyond the ulnar border of the hand. The wrist sign and thumb sign represent aspects of arachnodactyly (Figure 2).

### Table 2

<table>
<thead>
<tr>
<th>Systemic Scoring System for the Diagnosis of Marfan Syndrome</th>
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<tbody>
<tr>
<td><strong>Feature (Points)</strong></td>
</tr>
<tr>
<td>Chest deformity</td>
</tr>
<tr>
<td>Pectus carinatum deformity (2)</td>
</tr>
<tr>
<td>Pectus excavatum (1)</td>
</tr>
<tr>
<td>Chest asymmetry (1)</td>
</tr>
<tr>
<td>Dural ectasia (2)</td>
</tr>
<tr>
<td>Facial featuresa (1)</td>
</tr>
<tr>
<td>Foot deformity</td>
</tr>
<tr>
<td>Hindfoot deformity (2)</td>
</tr>
<tr>
<td>Plain pes planus (1)</td>
</tr>
<tr>
<td>Mitral valve prolapse, all types (1)</td>
</tr>
<tr>
<td>Myopia ≥3 diopters (1)</td>
</tr>
<tr>
<td>Pneumothorax (2)</td>
</tr>
<tr>
<td>Protrusio acetabuli (2)</td>
</tr>
<tr>
<td>Reduced elbow extension (1)</td>
</tr>
<tr>
<td>Reduced US/LS ratiob, increased arm/height, and no severe scoliosis (1)</td>
</tr>
<tr>
<td>Skin striae (1)</td>
</tr>
<tr>
<td>Spine deformity</td>
</tr>
<tr>
<td>Scoliosis (1)</td>
</tr>
<tr>
<td>Thoracolumbar kyphosis (1)</td>
</tr>
<tr>
<td>Wrist and thumb deformities</td>
</tr>
<tr>
<td>Wrist sign (1)</td>
</tr>
<tr>
<td>Thumb sign (1)</td>
</tr>
<tr>
<td>Wrist and thumb signs (3)</td>
</tr>
<tr>
<td>Maximum total score</td>
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</table>

LS = lower segment, US = upper segment

a Presence of three of the following features: dolichocephaly, enophthalmos, downsloping palpebral fissures, malar hypoplasia, retrognathia

b US length is the total arm span from each finger. LS is measured from the top of the symphysis pubis to the floor.

Scoliosis in patients with MFS progresses rapidly. The radiographic findings of MFS scoliosis are indistinguishable from those of adolescent idiopathic scoliosis (AIS). Non-surgical management of MFS scoliosis may involve the use of a brace; however, compared with AIS, MFS scoliosis is less responsive to bracing. Therefore, bracing typically is used only in skeletally immature patients with scoliotic curves between $15^\circ$ and $25^\circ$. This option can be offered to patients with greater degrees of curvature, although the low likelihood of success should be discussed. Curve progression may continue beyond skeletal maturity. Surgery should be considered for curves $>45^\circ$.

Techniques of curve correction are well documented, but surgeons should be aware of the higher revision and complication rates in patients with MFS compared with patients with AIS. In a retrospective case-controlled study, Gjolaj et al found that, compared with patients with AIS, patients with MFS scoliosis had higher rates of intraoperative cerebrospinal fluid leaks, considerably more implant-related complications, and more revision procedures as a result of fixation failure and spine fracture. Although the authors found no substantial difference in the estimated volume of intraoperative blood loss, other studies have reported higher blood loss and longer surgical times than in patients with AIS.

Formulation of an appropriate preoperative plan for spinal fixation is essential. Unique anatomic features of MFS include narrow pedicles, wide transverse processes, and vertebral scalloping. Adequate distal fixation, often into the pelvis or sacrum, may lessen the need for revision.

Dural Ectasia

Dural ectasia, or enlargement of the dural sac, may occur throughout the spinal column but most often is seen in the lumbosacral spine. It is a highly specific diagnostic feature of MFS and is present in more than two thirds of patients with MFS.

A study using a mouse model of MFS showed higher levels of TGF-β within the dura caused by fibrillin-1 deficiency. As the dural sac balloons, it may erode the surrounding bone, which already is weakened by the genetic mutation. These changes pose challenges to surgical fixation and create a high likelihood of fracture and dural injury.

Although pain is common in patients with dural ectasia, the exact cause of pain has not been established. Not every patient with dural ectasia experiences pain. Various causal theories exist, implicating pressure on the periosteum, erosion of the surrounding lumbosacral elements, traction of the nerve roots, direct pressure by the anterior meningocele on the abdominal organs, or microfractures of the sacrum from thinning of the bone.

Protrusio Acetabuli

As patients with MFS live longer, orthopaedic surgeons will face more challenges involving management of degenerative joint disease. One of the main causes of osteoarthritis in patients with MFS is protrusio acetabuli, which is one of the skeletal criteria for diagnosis in the revised Ghent nosology. This protrusion of the medial wall of the acetabulum into the pelvic cavity is initially asymptomatic. On an AP radiograph of the pelvis, the medial protrusion of the acetabulum beyond the ilioischial (Kohler) line is diagnostic for protrusio acetabuli. Other radiographic features include crossing of the teardrop by the medial acetabular wall and a center-edge angle of Wiberg $>40^\circ$.

Ligamentous laxity combined with bony abnormality may lead to joint degeneration, ultimately resulting in a symptomatic hip. In children with protrusio acetabuli, fusion of the

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triradiate cartilage in extreme protrusion (ie, a center-edge angle >45°) is a surgical approach that was advocated by Steel. In adults with this condition, total hip arthroplasty (THA) with appropriate bone grafting of the medial wall has provided symptomatic relief.

Not all patients with MFS and protrusio acetabuli require THA, but Thakkar et al showed that patients who needed THA because of pain had more severe protrusio acetabuli than did the MFS population as a whole. The authors also noted that, in patients with MFS, complications after THA (eg, dislocations, revision, infection, implant loosening) were not correlated with the presence of protrusio acetabuli. Dislocations likely are caused by impingement on the deeper acetabulum or ligamentous laxity, and implant loosening...
may be caused by MFS-related osteoporosis or osteopenia. No study has identified the ideal surgical approach for patients with ligamentous laxity. Thakkar et al reported good functional outcomes after THA for protrusio acetabuli in patients with MFS, with outcomes that were comparable to those in patients without MFS.

**Pes Planus**

Pes planus, or flatfoot deformity, is common in patients with MFS. The feet of these patients are longer and narrower than those of patients without MFS, making it difficult to find correctly sized shoes (Figure 6). Loss of the longitudinal arch is thought to be caused by underlying ligamentous laxity. Symptom management is the mainstay of treatment. Appropriate shoes and corrective orthoses may help to avoid or delay surgical correction. Scant research is available on the surgical techniques for pes planus or ligament augmentation, or on the outcomes of flatfoot reconstruction in this patient population.

**Lifestyle Considerations**

**Athletic Participation**

Patients with MFS can participate in low-impact athletic activities and those that do not require sudden, quick bursts of strength and energy. It is important to avoid activities that raise the heart rate or blood pressure and those that involve impact. Sports that are contra-induced include gymnastics and contact sports such as basketball, rugby, and American football, which pose a risk to the lenses of the eye and the aorta. Physical education activities that include these sports should be avoided by adolescent patients. The degree of restriction depends on the severity of disease suggested by the symptoms and imaging studies.

Despite much research, no definitive consensus exists about the appropriate cardiovascular and musculoskeletal screening for patients with MFS who want to compete in sports. Skeletal findings are typically the first recognized signs of MFS, and electrocardiography and echocardiography are the mainstays of screening for patients with skeletal findings. It may be impractical to use such tools unless substantial clinical suspicion exists for MFS. Further focus should be placed on the development and implementation of screening tools to identify patients whose participation in specific sports may be unsafe.

**Pregnancy**

Patients with MFS may elect to undergo preimplantation genetic testing before conception. Genetic counseling may aid in understanding the risks associated with the genetic transmission of MFS.

Pregnant women with MFS require strict surveillance throughout pregnancy. The hormonal and hemodynamic changes of pregnancy put pregnant women with MFS at high risk of aortic dilatation and even dissection. Avoiding hypertension during pregnancy is important, and β-blockers are an appropriate first-line therapy.

**Quality of Life**

MFS may create a substantial mental and physical burden on the patient, with different areas of concern for each person. According to Rao et al, in the United States, the quality of life of patients with MFS is lower than that of control subjects without the disease.

Pain is one of the most common concerns for patients with MFS. A recent systematic review of the literature estimated that the prevalence of pain in these patients is 47% to 92%. Adults with MFS report limited physical capacity, reduced endurance, and ultimately, depression and anxiety.

Through appropriate diagnosis and treatment, along with timely rehabilitation, patients are better able to lead productive lives. Optimal treatment of chronic pain in patients with MFS should be a focus of future research.

**Summary and Future Research**

MFS can restrict a patient’s career aspirations, athletic participation, financial security, and social life. Medical advances have enabled patients to live relatively normal life spans, but the symptoms of the disease occur over a longer period and often require treatment by orthopaedic surgeons, whose understanding of the disease can facilitate early diagnosis and timely treatment.

Orthopaedic surgery in patients with MFS is challenging. The risk for postoperative complications in this population is higher than that of patients without MFS. Patient comorbidities present additional challenges. It is imperative that...
cardiovascular abnormalities are considered as part of preoperative risk stratification.

Future research should focus on preventing and managing the osseous and soft-tissue manifestations of MFS. The knowledge of signaling pathways offers promise for new treatments. In addition, researchers should examine the optimal postoperative rehabilitative protocols for patients with MFS. A better understanding of the causes of MFS pain will enable a strong multidisciplinary treatment approach and result in a better quality of life for patients.

References

Evidence-based Medicine: Levels of evidence are described in the table of contents. In this article, references 12, 31, and 33 are level II studies. References 6, 17, 20, 22, 35, and 36 are level III studies. References 21 and 32 are level IV studies. References 2, 19, 25, 27, and 29 are level V expert opinion. References printed in bold type are those published within the past 5 years.


