Orthopaedic Management in Marfan Syndrome

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Abstract: Marfan syndrome (MFS) is a variable autosomal dominant connective tissue disorder affecting multiple organ systems. Causative mutations in the fibrillin-1 protein lead to dysregulation of transforming growth factor-β (TGF-β). A diagnosis of MFS can be made using systemic evaluation combining clinical and genetic features. Because the condition is characterized by a variety of musculoskeletal manifestations, orthopaedic surgeons may be the first provider patients will encounter. Common musculoskeletal manifestations of MFS include spine deformity, acetabular protrusion, limb length deformity, joint laxity, and foot pathology. Non-musculoskeletal manifestations include major cardiac and ocular conditions. Early identification is important for referral and prompt treatment of cardiovascular abnormalities, which can prevent premature mortality. As medical and surgical interventions have advanced, life expectancy for MFS patients has increased into the late 70s. We must remain vigilant, suspect diagnosis, and engage in multidisciplinary care to promote musculoskeletal function at advanced ages.

Key Concepts:

- Marfan syndrome is an autosomal dominant disorder, most commonly caused by mutations in fibrillin-1.
- Musculoskeletal manifestations, like scoliosis, acetabulum protrusion, pes planovalgus, and limb abnormalities are common, though cardiopulmonary and ocular problems have the potential to carry high mortality and morbidity.
- Scoliosis in Marfan syndrome progresses rapidly, is less responsive to bracing, requires application of different surgical tactics, is benefited by preoperative 3D imaging, and has higher rates of surgical complications.
- A systemic evaluation assessing a combination of clinical, familial, and genetic features is necessary to identify patients who possess ≥2 Marfanoid features and would benefit from further genetic and cardiopulmonary work up.
- Multidisciplinary perioperative management is essential to reduce morbidity and mortality, and for effective longitudinal care.

Introduction

Marfan syndrome (MFS) is a relatively common autosomal dominant disorder best known for its cardinal manifestations of long and narrow limbs and digits, superior lens dislocation, and potentially fatal cardiovascular abnormalities. There are many musculoskeletal findings in MFS patients because the causative mutation in fibrillin-1 disrupts extracellular matrix protein in connective tissues and affects growth factor bioavailability, which causes the associated musculoskeletal findings. These include generalized ligamentous laxity, scoliosis, chest deformity, protrusio acetabuli, foot deformities, hypermobility, dural ectasia, and low bone mineral density. This manuscript presents an overview of MFS pathogenesis, characteristic

syndromic manifestations, and the importance of multidisciplinary management.

Pathogenesis

MFS has an estimated prevalence of 2-3/10,000 persons with no known ethnic or gender predilection.[1] Many cases are inherited in an autosomal dominant pattern;[1] however, 25-30% represent new, sporadic mutation.[1, 2] MFS is a spectrum of connective tissue disorders most often caused by mutations in the fibrillin extracellular matrix protein, encoded by the FBN1 gene on chromosome 15.[3] Genetic testing for FBN1 mutations has a screening detection rate of 97%.[4, 5] While mutations in fibrillin have been identified in 66-91% of cases,[6] mutations in transforming growth factor β receptor-2 (TGFBR2) have been demonstrated to have similar phenotype.[7, 8]

Normally, fibrillin aggregates to form microfibrils to provide strength and elasticity of connective tissues. The expression of the altered gene inactivates fibrillin. The compromised mechanical integrity of tissues leads to the classic findings of ligamentous laxity, joint subluxation, dural ectasia, lens dislocation, and weakened arterial walls causing aortic dilation. Inactivated fibrillin increases growth factor availability in the extracellular matrix. Increased bioavailability of transforming growth factor β (TGF-β) is thought to increase cellular growth and cause increased longitudinal bone growth.[8, 9] This growth factor modulation results in the characteristic long, narrow features of Marfanoid habitus.[10]

Recognition

MFS affects multiple organ systems and is characterized by a variety of musculoskeletal manifestations.[1, 11-14] Major orthopedic conditions such as scoliosis, dural ectasia, acetabular protrusio, limb length deformities, foot deformity, joint hypermobility, and chest wall deformity can present early in life.[14-16] Orthopaedic surgeons may be the first provider to encounter an undiagnosed patient with MFS.[17] As such, the astute orthopaedic surgeon must remain vigilant and hold a high index of suspicion when encountering suggestive and possibly pathognomonic clinical findings.

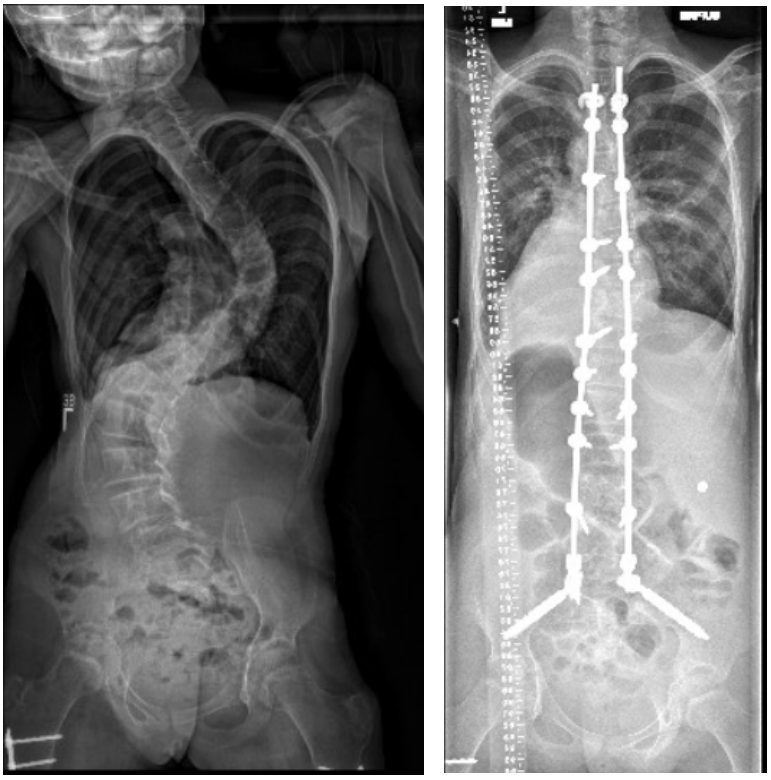

Figure 1. *PA radiographs of a 10-year-old girl with Marfan syndrome demonstrating pronounced scoliosis at a relatively young age before (a) and after (b) posterior spine fusion with a long construct that extends to the pelvis and includes all curves. Spine dysplasia is characterized by narrow, dysplastic pedicles, wide transverse processes, and short-segment scoliosis.*

Recurrent ankle or foot sprains and scoliosis are commonly among the first manifestations to be diagnosed. Ankle and foot pain may be indicative of pes planus or hindfoot deformity. Outward features raising concern for MFS include tall stature, long narrow limbs (dolichostenomelia) and arachnodactyly (long, slender digits). Skin striae and chest wall deformity are commonly present. “Thumb sign” and “wrist sign” testing can be rapidly performed. The thumb sign is positive if the patient’s thumb distal phalanx extends beyond the lateral border of the small finger when making a fist enclosing their thumb under their four

fingers. The wrist sign is positive when the patient's distal phalanges of their thumb and small finger overlap when wrapped around the opposite wrist. Lens dislocation or myopia can also be an early feature of the syndrome. The most serious, potentially life-threatening clinical feature is aortic root aneurysm or dilation, which may require immediate surgery. Early recognition with appropriate referral to specialists is important to prevent premature mortality and morbidity.[18]

Table 1: Diagnosing Marfan Syndrome Using the Revised Ghent Criteria[12, 13]

CRITERIA	DIAGNOSIS
Absence of Family History	
Aortic Root Dilation* AND Ectopia Lentis	Marfan Syndrome
Z Score ≥ 2	
Aortic Root Dilation* OR Ectopia Lentis, AND	
Z Score ≥ 2	
Systemic Score^ ≥ 7, or	Marfan Syndrome
FBN1 mutation	Marfan Syndrome
Presence of Family History, AND	
Ectopia Lentis	Marfan Syndrome
Systemic Score^ ≥ 7	Marfan Syndrome
Aortic Root Dilatation*	Marfan Syndrome
Z Score ≥ 2 above 20 years old	
Z Score ≥ 3 below 20 years old	

**Aortic Root Dilation Z Score as defined as the aortic diameter measured at the sinuses of Valsalva, when standardized to age and body size.*
^ *As described in Table 2, but excluding features suggestive of other connective tissue disorders (Shprintzen Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers Danlos syndrome) and in the absence of alternative genetic mutations (TGFBR1/2, SMAD3, TGFB2, TGFB3, COL3A1, other collagen biochemistry).*

Recognizing a constellation of physical and radiographic findings can aid the orthopaedic surgeon in diagnosing MFS.[12, 13] A formal diagnosis using the validated 2010 Revised Ghent Nosology (Table 1, 2 [12, 13]) can be made using a systemic evaluation combining clinical, familial, and genetic features. While the 2010 Revised Ghent Nosology distinguishes aortic root aneurysm and dislocated lens as cardinal features, the presence of a FBN1 mutation or a positive screening score > 7 of secondary features is diagnostic. The scoring system encourages serial evaluations and recognizes that phenotypic features can evolve and change over a patient's lifetime. When two or more highly specific features or three to four suspicious features are present, the orthopaedic surgeon should consider referral to genetics and cardiology specialists for secondary work up.[14]

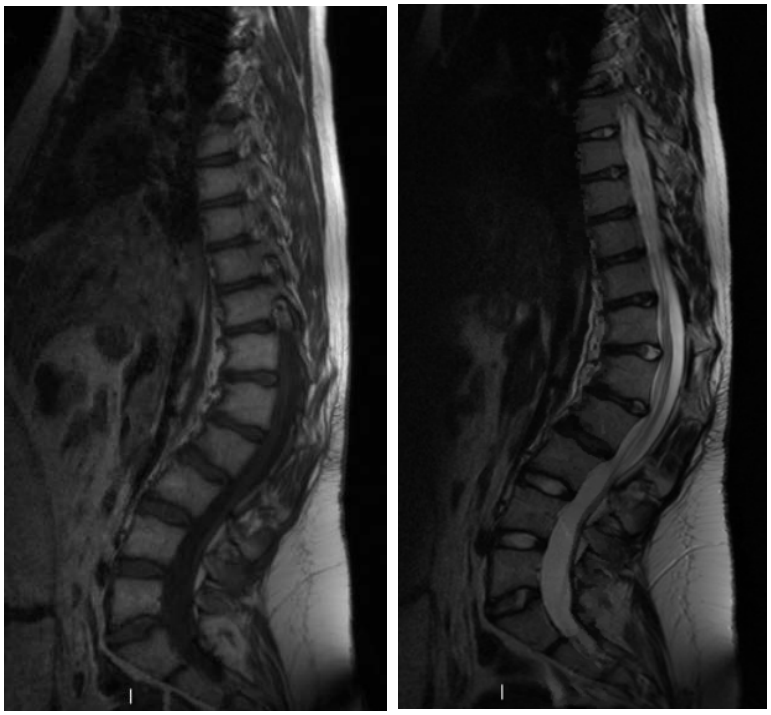

Figure 2*. Sagittal T1 (a) and T2 (b) weighted magnetic resonance images of the thoracic and lumbosacral spine of a 14-year-old boy with Marfan syndrome showing kyphosis and dural ectasia caudally.*

Spine Manifestations

Spine deformity is a common pathologic manifestation of MFS with case series reporting occurrences in 25-63% of patients.[15, 19, 20] While radiographic findings of

Table 2: Systemic Scoring System for the Diagnosis of Marfan Syndrome [12, 13]

FEATURE	SCORE (max 20)
Cardiac Abnormality	
Mitral Valve Prolapse	1
Ocular Abnormality	
Severe Myopia (>3 diopters)	1
Wrist and Thumb Deformities	
Wrist Sign	1
Thumb Sign	1
Wrist and Thumb Sign	3
Chest/Pulmonary Deformity	
Spontaneous Pneumothorax	2
Pectus Carinatum	2
Pectus Excavatum	1
Chest Asymmetry	1
Spine Deformity	
Scoliosis	1
Thoracolumbar Kyphosis	1
Dural Ectasia	2
Protrusio Acetabulae	2
Foot Deformity	
Hindfoot Deformity	2
Flat Foot	1
Skin Striae	1
Reduced Elbow Extension	1
Facial Features (3 of 5)	1
Dolichocephaly	
Downward slanting palpebral fissures	
Enophthalmos	
Retrognathia	
Malar hypoplasia	
Reduced Upper/Lower Segment AND Increased Arm Span/Height	1
Upper/Lower Segment < 0.85 in whites, <0.78 in blacks	
Upper Segment: Arm span, finger-finger	
Lower Segment: Pubis symphysis to floor	
Increased Arm Span/Height > 1.05	

scoliosis in MFS are similar to those of adolescent idiopathic scoliosis (AIS), management and rates of associated complications are different. There is high prevalence of double thoracic and triple majors with wide variation of sagittal profiles (Figure 1). Kyphosis is common and occurs in > 50% of patients [20, 21] (Figure 2).

Scoliosis in MFS progresses rapidly and is less responsive to bracing.[20, 21] Bracing can be used in the skeletally immature patient with smaller curves between 15-25 degrees.[22] Bracing can be attempted with greater levels of deformity; however, rates of converting to surgical treatment are high. Even with bracing, most patients with curves larger than 25 degrees and a Risser of 0-2 are likely to progress to meet surgical indications.[21] Surgery should be considered for patients with curves >45 degrees (Figure 1). Patients with curves > 50 degrees have progression rates of 3 +/- 4 degrees per year, which is significantly higher than that of AIS. Even after skeletal maturity, scoliosis in MFS patients progresses when curves are > 40 degrees. When advanced curvature occurs in the young patient, growing rod instrumentation can be a valuable tool (Figure 3). Extensible growing rods can effectively achieve adequate spine length, limiting the trunk disproportion that would otherwise result from early fusion or rapidly increased curve progression. Dual rods are helpful to control curvature and defer final fusion until skeletal maturity, or at least until chest cavity development.[23, 24]

MFS features several additional unique anatomic differences.[20, 22, 25] The spine surgeon must be mindful of narrow pedicles, wide transverse processes, and vertebral scalloping. Importantly, MFS has been associated with osteopenia.[26-28] These physical manifestations of weakened connective tissue may contribute to increased complication rates. Dural ectasia, commonly seen as dural sac enlargement at the lumbosacral spine, is a common and specific feature of

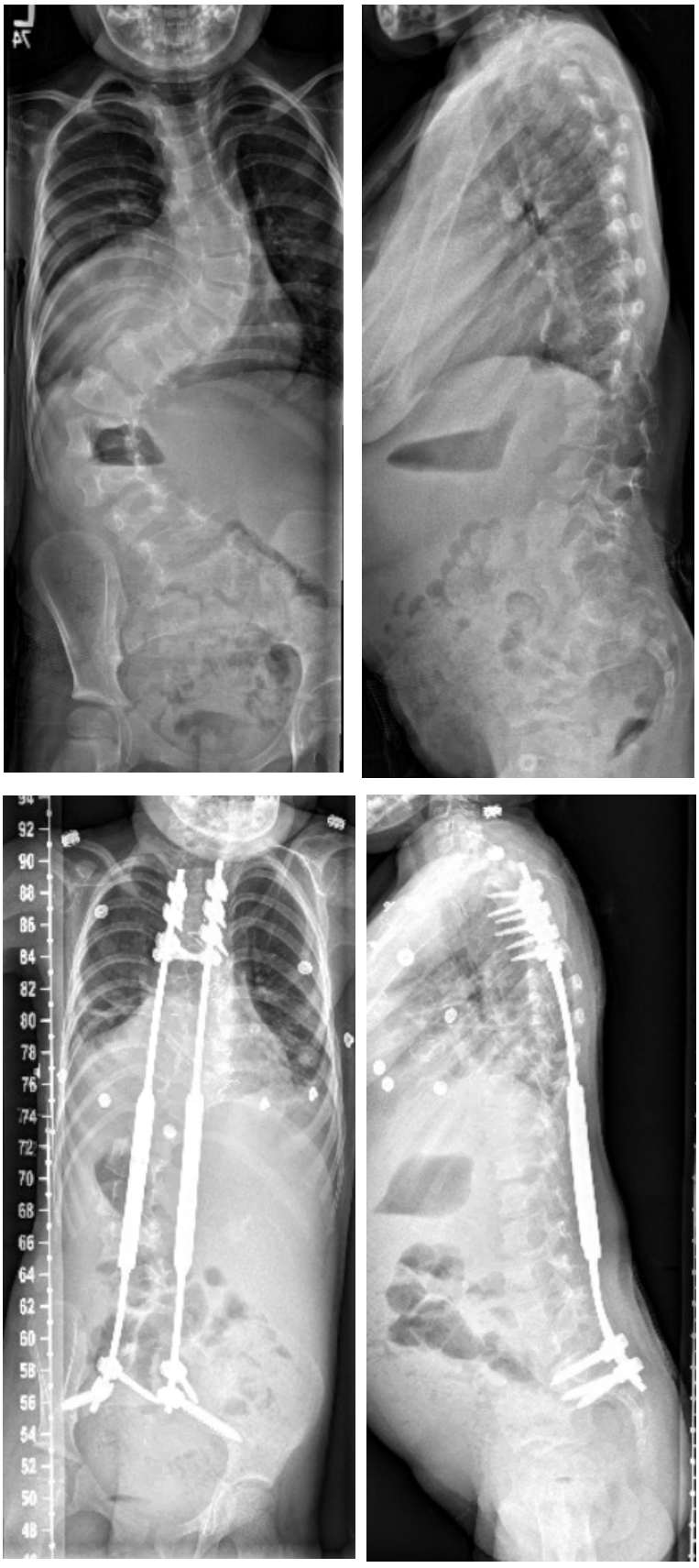

Figure 3. *Preoperative PA (a) and lateral (b) radiographs of a 3-year-old girl with Marfan syndrome and infantile scoliosis. PA (c) and lateral (d) radiographs of the same patient following treatment with growing rod instrumentation and iliac anchors at 3 years and 4 months.*

MFS [29-32] (Figure 2). The ballooned dural sac adds pressure to the already vulnerable surrounding vertebral bone. The pressure is manifested as bony erosion causing widened interpedicular distance, thinned laminae, and thin pedicles. The altered morphology increases the risk of fracture with instrumentation and the risk of tearing the fragile, thinned dura. Pressure on the periosteum and surrounding nerves can cause pain. Failure of fixation, pseudoarthrosis, intraoperative CSF leak, spine fracture, infection, distal degeneration, and revision occur more often in MFS than in AIS. [33-35]

Similarly, the management of spine surgery in MFS demands a different surgical tactic than AIS due to the inherently different soft tissue. Positioning in Trendelenberg can help decrease tension on the dura during lumbosacral surgery, which may prevent dural tear. Advanced imaging (CT scans) assessing bony anatomy can better characterize the dysplastic pedicles to better guide hook and screw instrumentation. Because traction can cause subluxation or over correction with subsequent risk of curve decompensation, traction should be used with caution. Selective thoracic arthrodesis for double curves is at risk of failure by "adding on" of curve at junctional fusion levels.[34, 35] To limit this particular means of failure, fusion should include all vertebrae within the Cobb angle extending to the sagittal stable zone [35] (Figure 1). Some advocate for increasing pedicle screw density in the fusion construct as a means of enhancing structural stability.[35, 36] Extending distal fixation to the pelvis or sacrum can also be effective in reducing the risk for revision (Figure 1). The apparent need for additional fixation may be a reason why some studies have associated MFS with higher volumes of intraoperative blood loss and longer surgical times. [35, 37]

Hip Pathology

Protrusio acetabuli, wherein the femoral head lies medial to the ilioischial line, is a skeletal criterion of MFS and is present on about 25% of patients [15, 38] (Figure 4[39, 40]). The presence and clinical significance of protrusio acetabuli in MFS patients is variable through life, steadily increasing then plateauing after the age of 20.[38] Although the hip is essentially asymptomatic in youth, secondary changes due to osteoarthritic loss of posterior inferior joint space can cause pain for some patients.[41]

Historically, Steel advocated for triradiate cartilage epiphysiodesis in pre-adolescent children with protrusion to arrest teardrop collapse and further acetabular deepening.[42] Triradiate epiphysiodesis was largely successful in restoring normal bony architecture and reducing protrusion. Even in the absence of pain or symptoms of restricted range of motion, triradiate closure may rarely be beneficial to patients whose medial acetabular protrusion is severe and progressive.[43] However, the development of symptomatic hip disease in older patients with MFS does not seem to be correlated to radiographic severity of acetabular protrusion.[43-44] Independent of protrusio, hip pain may be due to underlying cartilage abnormalities, which can lead to early arthroplasty in MFS patients.[44]

Some patients do progress to significant symptomatic hip osteoarthritis and can be indicated for surgery. If the patient is less than 40 years of age and has minimal arthritis, a valgus intertrochanteric osteotomy can be performed. Pain relief is achieved with a 20-30 degree corrective osteotomy by reducing the contact pressure of the medializing biomechanical vector driving the femoral head into the acetabulum.[45] If there is significant arthritis or the patient is older, arthroplasty is commonly offered. Patients who are offered arthroplasty tend to have more severe protrusion than the general MFS population.[44] Results of hip arthroplasty in MFS patients are notable for good functional outcomes but higher risk of dislocation, infection, loosening, and revision.[44] However, the presence or severity of protrusio itself was

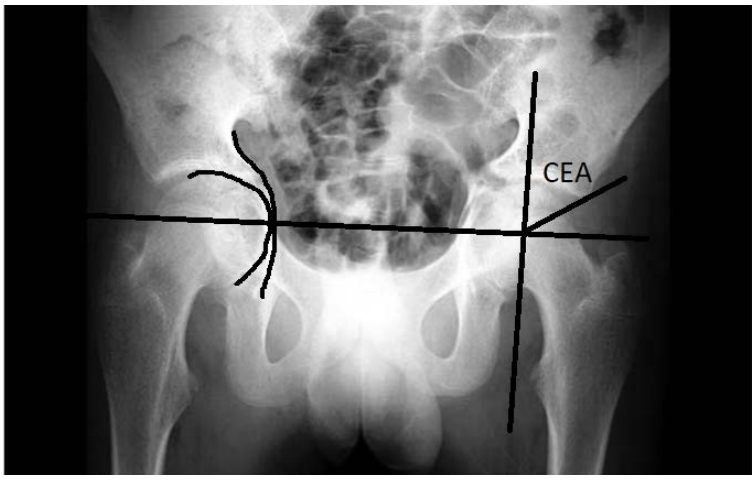

Figure 4. *AP pelvis demonstrating left acetabulum protrusio as defined by center-edge angle (CEA) greater than 40 degrees as measured by method of Steel. Right acetabulum protrusio is demonstrated by the method of Armbruster wherein the acetabular wall is shown to protrude ≥3 mm medial to the ilioischial (Kohler) line.*

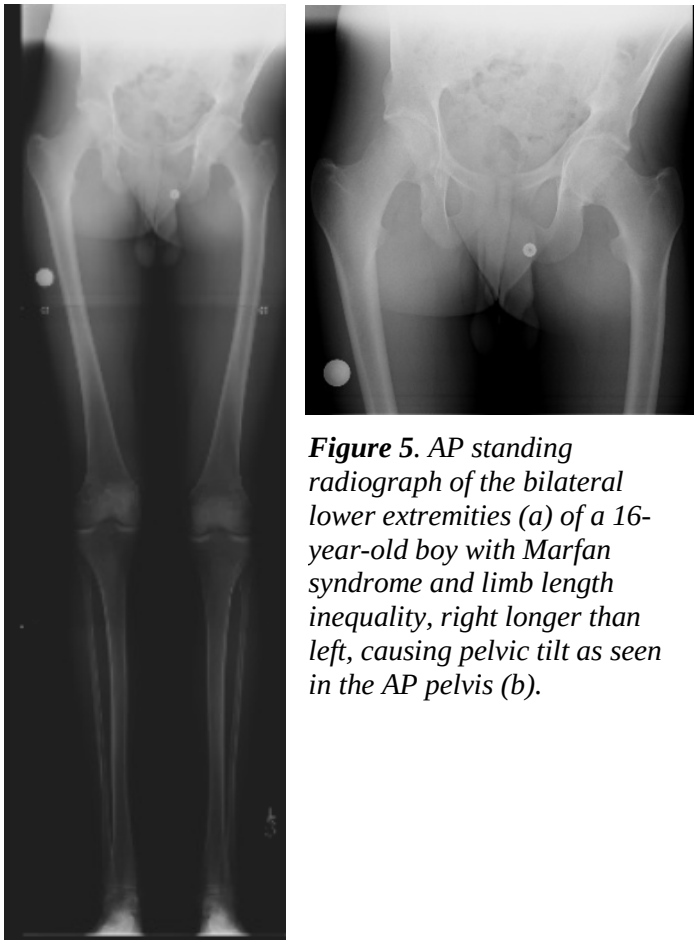

Figure 5*. AP standing radiograph of the bilateral lower extremities (a) of a 16-year-old boy with Marfan syndrome and limb length inequality, right longer than left, causing pelvic tilt as seen in the AP pelvis (b).*

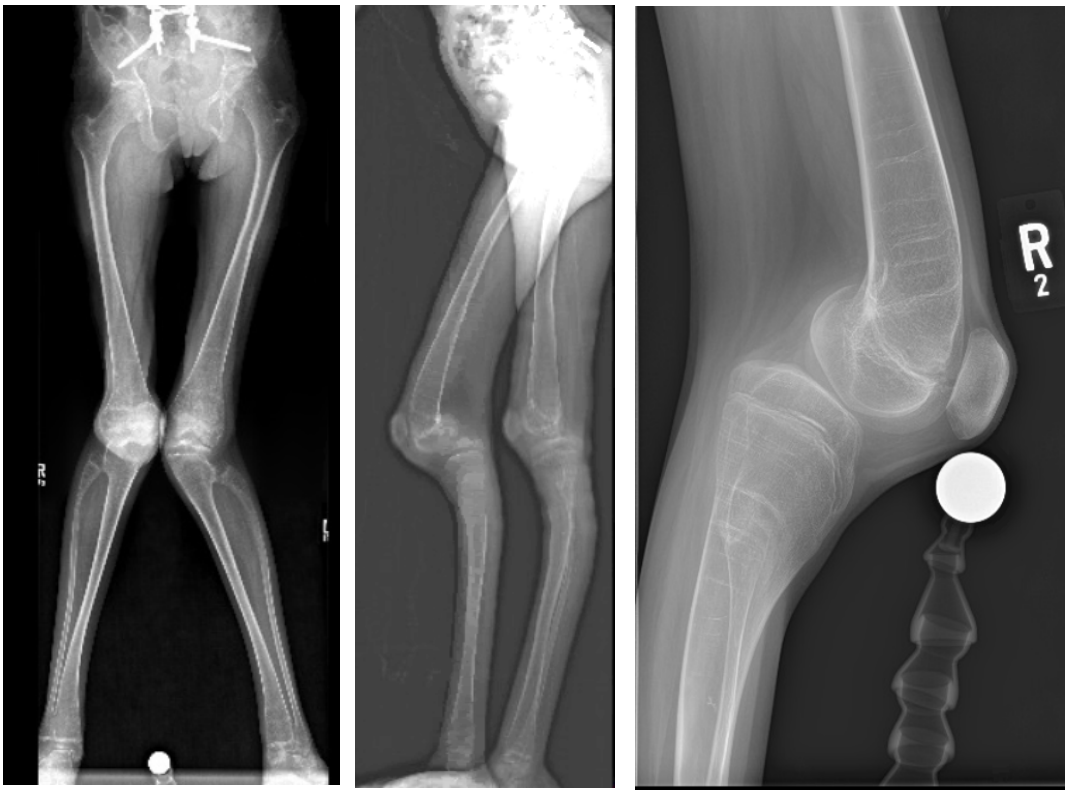

Figure 6. *Standing AP (a) and lateral (b) preoperative radiographs of a 12-year-old girl with Marfan syndrome characterized by severe lower extremity rotational and angular deformity with knee subluxation as seen in coned lateral right knee radiograph (c).*

not associated with increased risk of complications.[44] Regardless, the medial cavity should be built with non-structural bone grafting, such as from the femoral head, so that the acetabular prosthesis can be positioned laterally to reduce the stresses that can cause loosening.[45-47] Medial build-up and lateral positioning can also decrease risk of dislocation due to femoral neck impingement at end range of motion.

Limb Deformity

Limb length and angulation deformity are more common in MFS patients than the general population.[15, 20, 48-50] The pathologic loss of functional fibrillin in MFS causes downstream uncontrolled growth, placing physes at risk for angular deformities. Clinical screening should include assessment of length inequalities, angular deformities, and their relationship to spine deformity. When suspected, limb deformities can be diagnosed and characterized using full limb-length radiographs or full body scanograms (Figure 5, 6). In the lower extremities, slipped epiphyses, high riding patellae, and talipes extremities, recurrent shoulder and finger dislocations, arachnodactyly, and elbow flexion contracture are recognized features of MFS.[1, 11-13, 53] As length discrepancies increase beyond 2cm, cosmetic complaints, gait abnormalities, and distal contractures can become clinically significant, causing pain, scoliosis, and arthritic changes (Figure 5).[50] Greater limb length discrepancy is associated with increased structural scoliosis.[50, 54] Like other cases of limb deformity, treatment options for discrepancies greater than 2cm include heel lifts, epiphysiodesis, and limb length altering procedures.

Foot Deformities

Diagnostic skeletal criteria suggest that foot deformities are a common source of problems for patients with MFS (Figure 7, 8). The long, narrow morphology of patients' feet cause problems with comfortable shoe wear. While hindfoot deformity has been reported in about 20% of patients and pes planovalgus in about a third,[15, 55] it is unclear how problematic foot and ankle concerns are to patients. Ligamentous laxity is thought to result in the collapse of the medial arch. However, measures of generalized ligamentous laxity do not seem to be correlated to foot function or patterns of weight-bearing.[55] Literature on management of foot deformity in MFS is sparse and the mainstay of treatment is

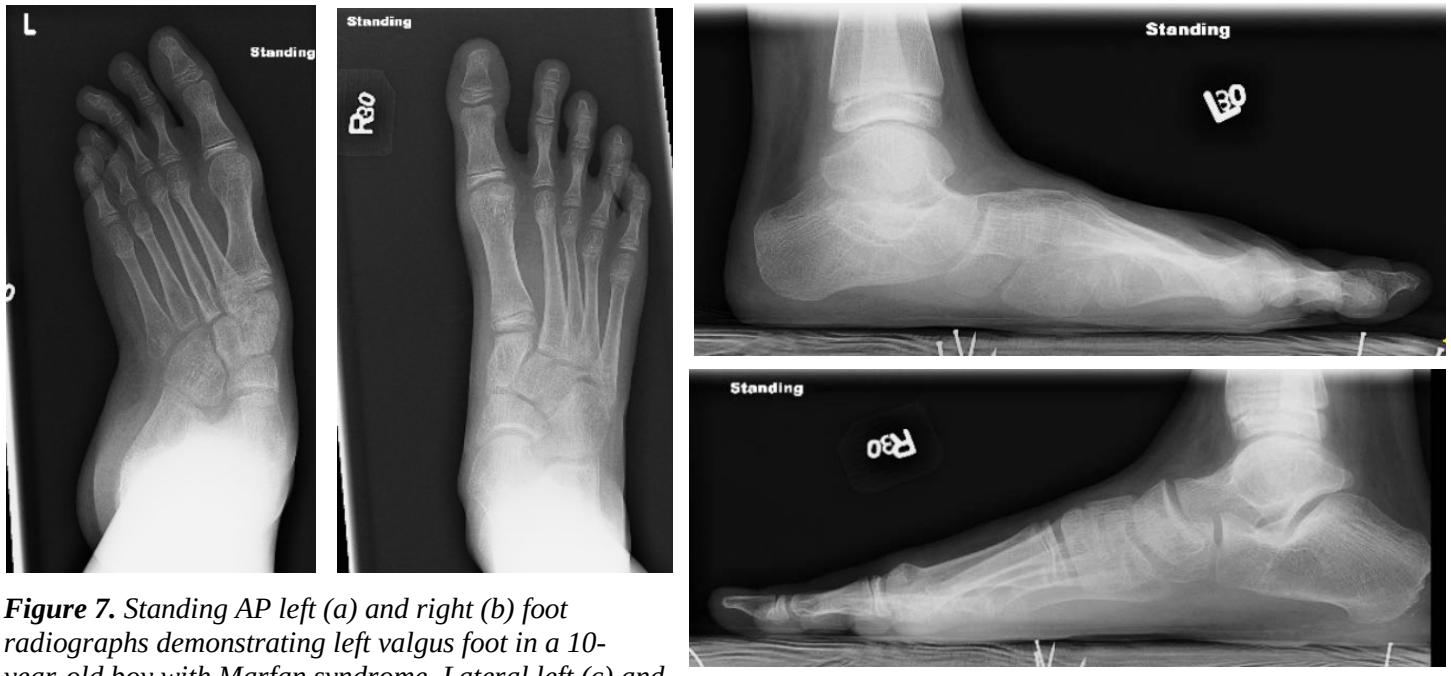

Figure 7. *Standing AP left (a) and right (b) foot radiographs demonstrating left valgus foot in a 10-year-old boy with Marfan syndrome. Lateral left (c) and right (d) standing foot radiographs from the same patient demonstrating left pes planovalgus.*

symptomatic management with nonoperative interventions, similar to other cases of flexible flatfoot. Surgical treatment should be indicated only if patients continue to be significantly symptomatic after failed nonoperative treatments. Initial, nonoperative treatment options include activity modification, immobilization, shoe orthoses, physical therapy exercises, and nonsteroidal anti-inflammatory medications as needed. Given the underlying ligamentous laxity in MFS, isolated soft-tissue procedures are thought to be of limited to no benefit. However, there is little literature regarding surgical techniques or outcomes of ligament augmentation or bony surgical correction.

Multidisciplinary Care

For the diagnosis and management of MFS, it is often necessary to have collaboration among pediatricians, cardiac surgeons, ophthalmologists, orthopaedic surgeons, geneticists, and cardiologists. A multidisciplinary approach is necessary for successful long-term management of the syndrome and for optimization prior to surgical intervention.

Because of possible significant cardiopulmonary comorbidities, a thorough preoperative evaluation should be performed prior to orthopaedic surgery. Evaluation should address the presence and degree of aortic dilation, valvular disease, and need for anticoagulation management. The most significant causes of morbidity and mortality in MFS patients are cardiovascular complications due to aortic dilation, dissection, or rupture. Without prompt recognition and early prophylactic surgery, approximately 50% of MFS patients die by the age of 40 secondary to aortic dilation.[56] Other cardiopulmonary manifestations include mitral valve prolapse, pulmonary artery enlargement, and left ventricular dilatation. Echocardiography is the most accessible modality for cardiopulmonary assessment. Medical optimization with beta-blockers is the current standard, though medications blocking the angiotensin II Type 1 receptor are also being investigated.[57-60]

Fibrillin deficiency can cause flaccid or redundant airways, placing the patient at risk for premature airway closure or obstruction and altered FEV1 and FVC.[61-67] Spontaneous pneumothorax, blebbing, and emphysema are characteristic pulmonary features of MFS.[61-67]

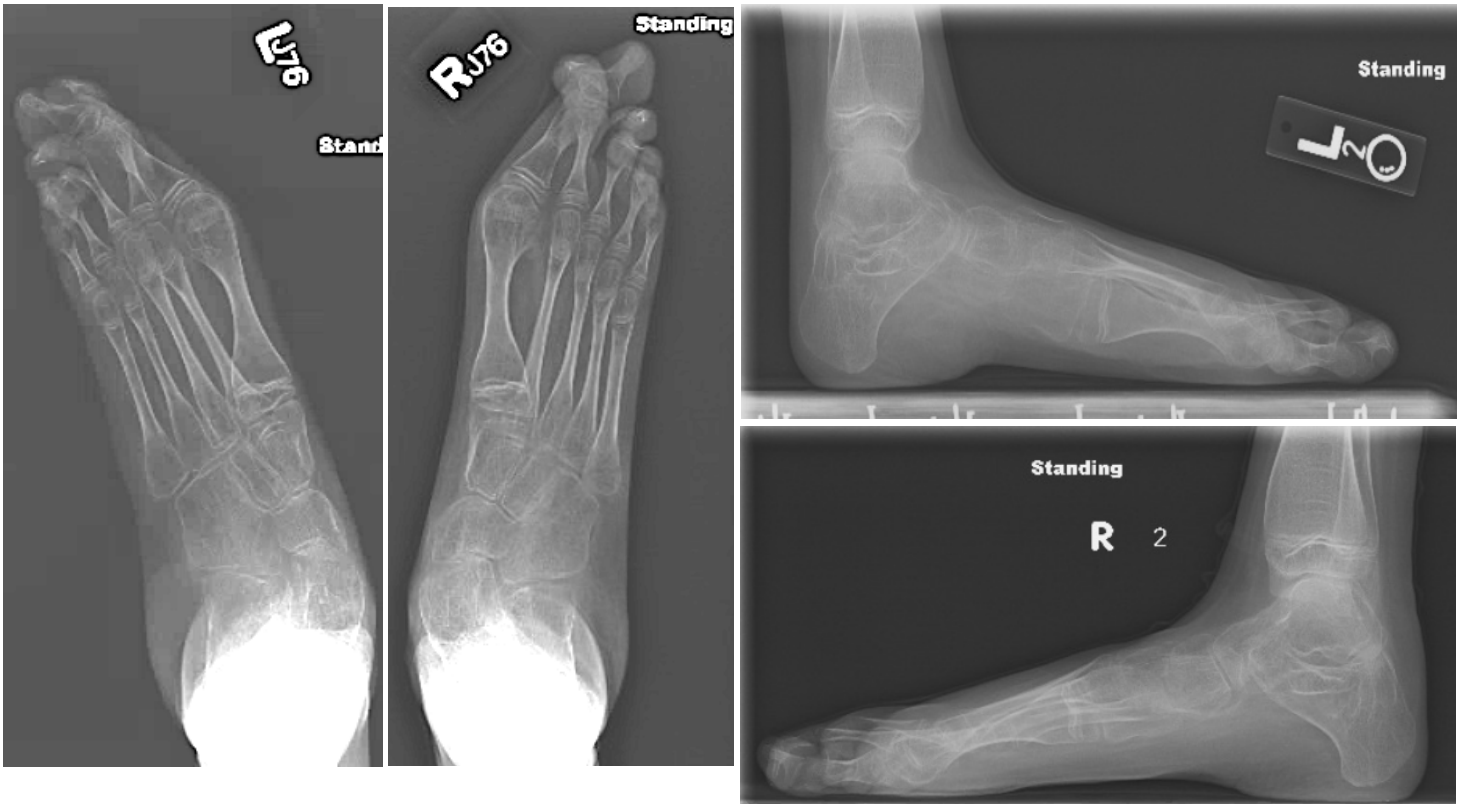

Figure 8*. Standing AP left (a) and right (b) foot radiographs demonstrating foot abduction in a 12-year-old boy with Marfan syndrome. Lateral left (c) and right (d) standing foot radiographs from the same patient demonstrating talipes calcaneus.*

Regular ophthalmic examinations are the standard of care for patients with MFS. Superiorly dislocated lens is a cardinal feature of MFS and may be the presenting symptom for patients. Myopia, glaucoma, cataracts, and retinal detachment are additional ocular manifestations.

Parents of children with MFS often have questions regarding safe sports restrictions. Generally, low-intensity, low-impact exercises are safe for patients including swimming, biking, or light jogging.[68-70] However, high-intensity exercises with sudden changes in movement or direction, or risk of direct impact should be avoided.[68-70] Such precautions are important to protect the aorta and lens. Avoiding common sports like gymnastics or tumbling, dodgeball, basketball, football, and soccer is recommended. School physical education activities should be modified. When exercising, the level of exertion should be limited to < 50% of capacity and heart rate maintained below 110 beats per minute. If patients already have significant cardiopulmonary features, restrictions may be stricter.[68-70]

Summary

Musculoskeletal differences are common in patients with MFS. While many outward manifestations can be easily assessed, cardiopulmonary manifestations are more insidious and carry greater morbidity and mortality, prompting frequent assessment.

Due to medical advances, life expectancy in MFS is improving, leading to more time for musculoskeletal pathology to become symptomatic. The orthopaedic surgeon must have a high index of suspicion and low threshold for specialist referral (genetics and cardiology) when two or more Marfanoid features are apparent by history, physical, and imaging. Multidisciplinary perioperative management is essential for safety and effective longitudinal care.

Additional Links

1. The Marfan Foundation
https://www.marfan.org/

2. "Healthy Spine and Limbs in Patient's with Marfan Syndrome," sponsored by The Marfan Foundation, featuring Paul Sponseller and Adam Bitterman
https://www.vumedi.com/video/healthy-limbs-feet-spine/

3. "Characteristics and Long-Term Outcomes in Adults with Marfan Syndrome and Ascending Aorta Surgery," sponsored by Cleveland Clinic Heart, Vascular and Thoracic Institute, featuring Lars Svensson and Milind Desai
https://www.vumedi.com/video/characteristics-and-long-term-outcomes-in-adults-with-marfan-syndrome-and-ascending-aorta-surgery/

4. "Healthy Feet and Quality of Life in Patient's with Marfan Syndrome," sponsored by The Marfan Foundation
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