CHAPTER **10**

MARFAN SYNDROME

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In 1896 at the Société Médicale des Hôspitaux de Paris, the first professor of pediatrics in France, Antoine Marfan, presented a 5-year-old girl as the first possible case of what is now known to be Marfan syndrome.[1] Marfan syndrome is an inherited connective tissue disorder that affects multiple systems in the body. The inheritance pattern is that of an autosomal dominant nature affecting as many as 1 to 4 per 1,000.[2] Marfan syndrome has been linked to the fibrillin-1 gene located on chromosome 15, FBN 1.[3] Incomplete penetrance of the gene often occurs resulting in a variable phenotype. Approximately 15-33% of cases occur with no family history thus representing new mutations.[2-4] Abnormalities in synthesis, secretion, or matrix incorporation of fibrillin leads to the clinical manifestations of Marfan syndrome.

Marfan syndrome is in a class of heritable disorders characterized by matrix protein mutations. The proteins affected include, but are not exclusive to, fibrillins, collagens, and elastins. The group of heritable connective tissue diseases (HCTDs) presents with multi-system effects which are often similar.[5] Particular attention needs to be taken when dealing with the HCTDs, particularly with Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, and benign joint hypermobility syndrome.[5] For correct diagnosis, the entire gamut of clinical manifestations must be evaluated to distinguish the identifying characteristics of Marfan syndrome from those of the other HCTDs.

BIOCHEMISTRY

FBN 1 mutations can be identified in up to 70% of affected people.[3] The FBN 1 gene encodes the glycoprotein fibrillin which is a major component of elastic microfibrils in the extracellular matrix of many types of connective tissue, especially that of bone, ligament, tendon, and dermis.[3,6] Microfibrils are made-up of end to end polymers of fibrillin molecules.[3] In a study by Dallas et al., fibrillin-1 was colocalized to the outer periosteum and the osteoblastic layer adjacent to the new bone surface in cultured human fetal 72-day-old long bones.[3] The FBN 1gene extends 110 kb, contains 65 exons, and encodes a messenger RNA molecule measuring 10 kb.[3] As many as 135 mutations have been identified in the fibrillin gene.[6] Missense mutations in exons 24 to 26 or skipping of exons 31 or 32 have been proposed to be the cause of the severe neonatal form of the disease.[3]

DIAGNOSTIC CRITERIA

The Berlin nosology was the first attempt to classify Marfan syndrome.[1,5] For clinical diagnosis according to the nosology, excluding a positive family history, certain criteria must be present for diagnosis. The patient must display major criterion in two major systems with involvement of a third organ system.[3] Patients with a positive family history require one major criterion in one organ system and involvement of a second organ system.[3] Approximately 15-33% of cases occur with no family history thus representing new mutation.[2-4]

Hypermobility, although not a major criterion for diagnosis, is frequently found in Marfan syndrome. The result can be debilitating and requires strict orthopedic and podiatric assessment and management. Classification of the extent of hypermobility has been attempted to aid in the level of intervention required. Two scales that are used to attempt to quantify joint mobility include the Beighton method and the Contompasis approach.[2] The Beighton method is based on a maximum score of 9 and involves 5 criteria (Table 1).[7,8] The Contompasis method is based on a maximum score of 72 and involves criteria that involve the level of mobility in the entire body with 6 tests (Tables 2A-2F).[9] These tests, although neither is considered the universal template per say, can offer a correlation between the level of hypermobility and the diagnosis of Marfan syndrome.

CLINICAL PRESENTATION

The cardiovascular, skeletal, and ocular systems are the major organ systems which are principally involved in Marfan syndrome. Other systems affected include the lungs, central nervous system, and skin.[6] Lower extremity manifestations are often present and frequently symptomatic. Hypermobility is a common finding and is usually confined to the smaller and most peripheral joints.[10] Currently, more advances are being made in the treatment of cardiovascular complications resulting

Table 1

NET BEIGHTON HYPERMOBILITY SCORE

	Right	Left
Passively dorsiflex metacarpophalangeal joint 5 to ≥ 90°	1	1
Oppose the thumb to the volar aspect of the ipsilateral forearm	1	1
Hyperextend elbow to ≥10°	1	1
Hyperextend knee to ≥ 10°	1	1
Place hands flat on floor w/o flexing knees	1	
Total score	**9**	

Table 2A

CONTOMPASIS HYPERMOBILITY SCORE: TEST 1= THUMB TO WRIST TEST (TOTAL SCORE 72 POINTS)

Description	Normal	Pts	Low Hypermobility	Pts	Moderate Hypermobility	Pts	High Hypermobility	Pts
Passive opposition of thumb to flexor aspect of forearm	30-75°	2	Thumb touches forearm	4	Thumb digs into forearm easily	5	Thumb overlaps outside of forearm	6

Table 2B

CONTOMPASIS HYPERMOBILITY SCORE: TEST 2= METACARPOPHALANGEAL JOINT (MCPJ) HYPEREXTENSION

Description	Normal	Pts	Low Hypermobility	Pts	Moderate Hypermobility	Pts	High Hypermobility	Pts
Passive DF of MCPJ 5	30-85°	2	90-100°	4	100-120°	5	≥120°	6

Table 2C

CONTOMPASIS HYPERMOBILITY SCORE: TEST 3= ELBOW EXTENSIBILITY

Description	Normal	Pts	Low Hypermobility	Pts	Moderate Hypermobility	Pts	High Hypermobility	Pts
Passive hyperextension of elbow	0-5°	2	10-16°	4	16-20°	5	≥20°	6

Table 2D

CONTOMPASIS HYPERMOBILITY SCORE: TEST 4= KNEE EXTENSIBILITY

Description	Normal	Pts	Low Hypermobility	Pts	Moderate Hypermobility	Pts	High Hypermobility	Pts
Passive hyperextension of knee	0-5°	2	10-16°	4	16-20°	5	≥20°	6

Table 2E

TEST 5= FORWARD BEND

Description	Normal	Pts	Low Hypermobility	Pts	Moderate Hypermobility	Pts	High Hypermobility	Pts
Hyperflexibility of spinal column	No contact w/ground	2	Fingertip touch to ground	4	Fingers touch ground	5	Wrist or forearm to ground	6

Table 2F

TEST 6 - ANKLE DORSIFLEXION AND CALCANEAL STANCE MEASURING REARFOOT (RF) EVERSION*

Description	Normal	Pts	Low Hypermobility	Pts	Moderate Hypermobility	Pts	High Hypermobility	Pts	High Hypermobility	Pts.
Foot flexibility test	0-2° RF eversion	2	3-5° RF eversion	4	6-10° RF eversion	5	10-15° RF eversion	6	≥15°	8

in more noticeable musculoskeletal manifestations including hypermobility and lower extremity deficits. There is a wide variety of clinical expression of Marfan syndrome with some of those affected demonstrating pathology in only one or two systems.

As many as 90% of those affected with Marfan syndrome demonstrate cardiovascular abnormalities.[11] These findings may not always be evident requiring extensive diagnostic testing including echocardiography and magnetic resonance imaging. The most common cause of sudden death in Marfan syndrome is aortic root aneurysm, rupture, or dissection.[12] Mitral valve prolapse and mitral regurgitation are also seen.[1,13] Due to the increased awareness of these cardiac pathologies and characteristic clinical findings, early detection has been possible thus increasing life expectancy of patients.

Skeletal manifestations are diverse and frequently apparent. The most evident external feature of the disease is that of increased length of tubular bones.[11] This creates elongated appearance of extremities (dolichostenomelia), increased height, and long fingers (arachnodactyly, "spider fingers").[4,11] Patients also present with inward displacement of the sternum (pectus excavatum), scoliosis, and frequent atlantoaxial subluxation.[1,3] Scoliosis presents in approximately 60% of patients with Marfan syndrome.[3] More than 50% of patients have demonstrated atlantoaxial subluxation.[3] Tallroth et al. noted the presence of multiple vertebral abnormalities including biconcave vertebra, transition vertebra, and increase transverse process distance.[14] Alterations in bone mineral density are also significantly noticeable in Marfan syndrome patients. Kohlmeier et al. noted that abnormal

fibrillin may result in deficits in the biomechanical properties of bone by interfering with the distribution of mechanically induced strain that occurs during skeletal development, or by altering mineralization of osseous matrix.[3] Although most patients demonstrate decreased bone mineral density, not correlation can be made with fracture occurrence or risk in most cases.[3]

Ocular abnormalities are often present and have become key to proper diagnosis. Ectopia lentis is the most common feature seen. It requires full papillary dilation and slit-lamp examination and can occur in any direction.[1] Other findings include flatness of the cornea, increased axial length of globe, megalocornea, and hypoplastic iris or ciliary muscles resulting in myosis.[1,3]

Dural ectasia is widening or ballooning of the dural sac and is a major criterion for Marfan syndrome.[3] The caudal portion of the lumbosacral region is most commonly involved. This happens to be the area at which the cerebral spinal fluid pressure is the greatest in the upright patient.[3] This can cause headaches, back pain, and other neural symptoms with resultant bony erosion or anterior meningoceles.[3]

Striae atrophicae, papyraceous scars, and decreased wound healing are found to be quite substantial in Marfan syndrome.[2] The fibrillin alterations can account for these findings. These dermal manifestations, while significant, tend to be not as large or as common as in EDS.[2]

Locomotor and lower extremity symptoms are many and often prove to be debilitating. Grahame et al. found that 19 of 27 children and 46 of 48 adults demonstrated arthralgia, back pain ,and ligamentous injury.[2] There was also found to be a direct correlation between age and severity of symptoms.[2] Absence of subcutaneous fat and muscle can also account for the long, trim frame of Marfan patients.[11] Some authors have recently begun to draw attention to ligament laxity as one of the causes of premature osteo-arthritis.[8,15,16] Degenerative joint disease can be seen in the late stages of Marfan syndrome due to early hypermobility and spinal deformities.[2]

Although not a major criterion for diagnosis of Marfan syndrome, hypermobility is noted to be present in a large proportion of patients. Giam et al. found that 19 of 27 children and 46 of 48 adults demonstrated hypermobility or related complaints as a result of the hypermobility including joint arthralgia, back pain, and ligamentous injury.[3] In contrast to EDS, physical limitation due to hypermobility does not seem to be a common complaint.[3] Some authors have postulated that the increased mobility in the scoliotic curve may be due to apparent connective tissue alternations. Hypermobility can also lead to angular deformities. Further consequences are increased occurrence of traumatic dislocations, recurrent dislocation, subluxations, and joint effusions.[17]

Lower extremity manifestations of Marfan syndrome include hypermobility, ligamentous laxity, skin abnormalities, pes planus, and precocious osteo-arthritis particularly in the small joints of the feet.[3,8] A wide variation in joint presentation of the extremities is seen, from congenital contractures to hypermobility.[8] When motion is in excess as the joint due to ligamentous laxity, resulting angular deformities are seen.[9] Most angular deformities are seen at the interphalangeal and metatarsophalangeal joints resulting in hammertoes.[10] Pes planus most likely occurs due to the instability of joints and ligamentous structures. Decreased bone quality and diminished osseous formation due to alterations in bone mineral density can also lead to pes planus. Other lower extremity symptoms occur secondarily to manifestations in the rest of the body, especially abnormalities in the vertebral column. Decreased proprioception due to ophthalmologic deficits can lead to further pedal injuries.

DIAGNOSIS

Marfan syndrome encompasses such a plethora of possible characteristics that diagnosis can often prove challenging. There are certain patients that are mildly affected and make diagnosis difficult, while on the other end of the spectrum there are severely affected patients with possible lethal outcomes.[13] Diagnosis relies almost entirely on clinical presentation. During infancy, diagnosis may be more apparent while other times it may not be possible until the second or third decade.[11] Due to the possible severity of the disease, patients should undergo genetic, cardiologic, and ophthalmologic evaluation.[7] This is especially true for any child suspected of having Marfan syndrome.[7] As part of the evaluation, diagnostic studies that are commonly employed include standard radiographs including the cervical spine, CT, MRI, and BMD analysis. Through identification of defects in the fibrillin gene, a more certain diagnosis is assured. Before a systematic investigation of the effects of defective microfibrils is performed, all the clinical manifestation must be identified.[2] Once all modalities have been utilized, correlation with clinical history and presentation must be made.

Distinguishing between the HCTDs often proves difficult (Tables 1-4). There is considerable overlap in presentation even in cardinal features of which include marfanoid habitus of Marfan syndrome, hyperextensible skin of EDS, and brittle bones of OI.[5] BJHS presents with wider overlap of features, yet much less severity.[5] For

example, aortic dissection, as seen in Marfan syndrome, is not found in BJHS hence the "benign" in its name. Even though a patient may present with excess laxity of joints and hypermobility which suggests Marfan syndrome, the presence of other cutaneous manifestations such as bleeding tendencies and tissue fragility points to EDS. Incorrect diagnosis has possible life-threatening results. Thus, the keystone to diagnosis is defining the characteristic(s) that makes the disease its own.

DIFFERENTIAL DIAGNOSES

Many disorders must be considered when a patient presents with the possible criterion for Marfan syndrome. There are a number of connective tissue disorders defined primarily by one of the major manifestations of Marfan syndrome. This emphasizes the necessity for extensive evaluation to establish correct diagnosis. Each line of evaluation must consider the multiple expressions of such disorders. These variations must be thoroughly investigated to rule out all possible syndromes.[5]

Disorders that must be considered are, in addition to the HCTDs, Achard's syndrome, Homocysteinuria, Rheumatic Fever.[2,3] Homocysteinuria is a highly probable differential diagnosis in a patient presenting with possible Marfan syndrome, yet the presence of mental retardation, autosomal recessive inheritance, decreased mobility in the hand joints, arterial and venous thrombosis, malar flush, and increased urine excretion of sulphydryl containing compounds allows one to rule it out as the possible causative disorder[10] Inflammatory arthropathies and neurological diseases such as polymyositis, tabes dorsalis, and myotonia congenita must also be considered.[15] Neurologic changes can result in "flail joints" leading to traumatic synovitis and secondary osteoarthritic-like changes.[15] Congenital contractural archnodactyly (CCA) and familial mitral valve prolapse syndrome each present with one of the major criterion in Marfan syndrome diagnosis and must be excluded.[5]

CONCLUSION

It can not be stressed enough the importance to the physician and the patient of being able to distinguish what is and what is not Marfan syndrome. Physical, mental, social, and occupational consequences are to be taken seriously by those diagnosed and those that diagnose. The variability in clinical presentation and severity of the disorder requires full knowledge of the disorder and thorough evaluation. A step-wise approach should be taken when dealing with each patient, addressing each condition as its own and managing it accordingly. Particular attention should be paid to the lower extremity as inevitable manifestations are found. Podiatric management should be taken seriously and addressed early to prevent further symptomatology.

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