Syndromes-Pathologies

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Marfan syndrome

Syndrome de Marfan

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I. INTRODUCTION

Patients with MARFAN´s syndrome are a clinically diverse group; they have a combination of dolichostenomelia, arachnodactyly, pectus deformities of the chest, mitral or aortic regurgitation, ectopia lentis and mild joint laxity. Other evidence of a generalized connective tissue disorder may be present such as scoliosis and skin striae. In 1902, ACHARD named the syndrome arachnodactyly, although MARFAN considered this characterization too limited. BOERGER in 1914 identified the characteristic ocular anomaly of lens dislocation (ectopia lentis). WEVE in 1931 demonstrated that this syndrome was an autosomal dominant condition. It was only after the identification of associated cardiac anomalies by BAER and colleagues in 1943 that the description of the major features of MARFAN´s syndrome was complete. Ironically, the diagnosis of MARFAN´s first patient has been challenged by HECHT and BEALS, who believe that GABRIELLE's condition was more like BEAL´s syndrome, because she apparently lacked the typical ocular and cardiac anomalies associated with MARFAN´s syndrome. MARFAN´s syndrome is transmitted in an autosomal dominant pattern of inheritance. There is great variability in the nature and severity of clinical manifestations, and an unwary physician may not recognize the syndrome in mildly affected patients. Family history of MARFAN´s syndrome is an important diagnostic criterion; the incidence of spontaneous mutations is thought to be between 15-30%. The lack of specific laboratory test to confirm the diagnosis of MARFAN´s syndrome and the variable clinical expression of the disorder, including mild manifestations, make it difficult to estimate its incidence with certainty.

II. CLINICAL FEATURES

A patient with classic florid MARFAN´s syndrome is easily recognized as an unusually tall, lanky individual with arachnodactyly, disproportionate long arms, chest wall deformity, severe myopia, and a loud cardiac murmur. Patients with MARFAN´s syndrome are typically tall, usually attaining height greater than 6 feet in adult life and have disproportionately long, thin limbs. The distal bones of the limbs exhibit the excess length most strikingly, resulting in long, slender hands and feet with spider-like digits (arachnodactyly) (Figure 1).

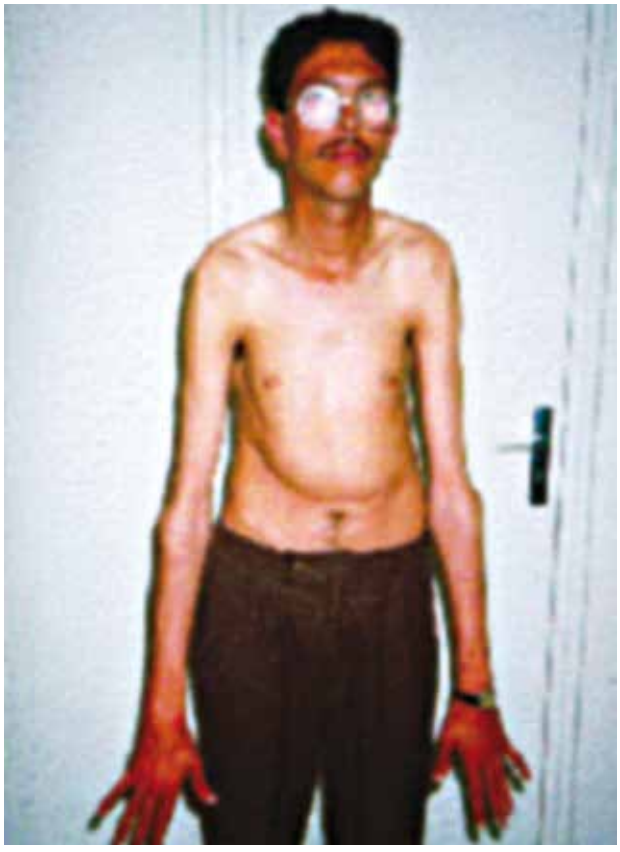

Figure 1*: A-35- year-old patient with Marfan´s syndrome, he manifested the whole clinical criteria of unusually tall, lanky individual with arachnodactyly, disproportionate long arms, chest wall deformity, severe myopia, and was operated for dissecting aortic aneurysm. The patient attained the height greater than 6 feet in adult life and has disproportionately long, thin limbs. The distal bones of the limbs exhibit the excess length most strikingly, resulting in long, slender hands and feet with spider-like digits (arachnodactyly).*

The ratio of the upper body segment (measures from the top of the symphysis pubis to the top of the head, or by subtracting the measurement of the lower body segment from the total height) to the lower body segment (measured from the sole to the top of the symphysis pubis) is abnormally low (the upper body-lower body ratio is 0.93 in the normal adult population). In addition, the arm span usually exceeds the patient's total height (Figure 2).

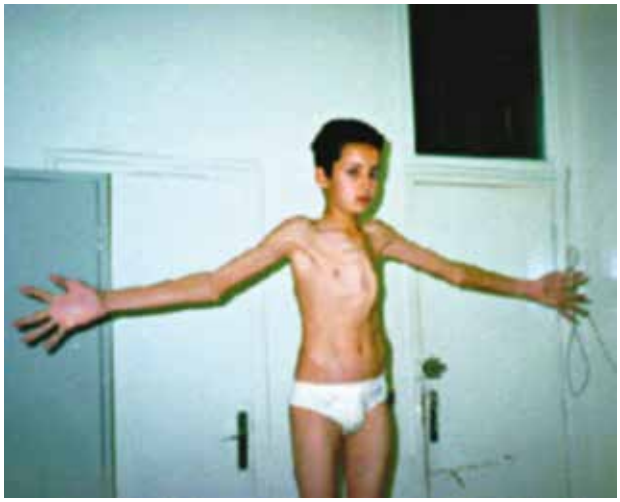

Figure 2: *The phenotype of Marfan´s syndrome in a 14-year-old boy, note that the ratio of the upper body segment (measures from the top of the symphysis pubis to the top of the head, or by subtracting the measurement of the lower body segment from the total height) to the lower body segment (measured from the sole to the top of the symphysis pubis) is abnormally low (the upper body-lower body ratio is 0.93 in the normal adult population). In addition, the arm span usually exceeds the patient's total height. Note the carinum chest.*

Skeletal abnormalities such as pectus excavatum are a common manifestation and are caused by excessive longitudinal growth of the ribs. The anteroposterior diameter of the thoracic cage is reduced. Significant joint laxity is another hallmark of the disease. Dislocations of the hip, either developmental or presenting later in life are not uncommon feature (Figure 3).

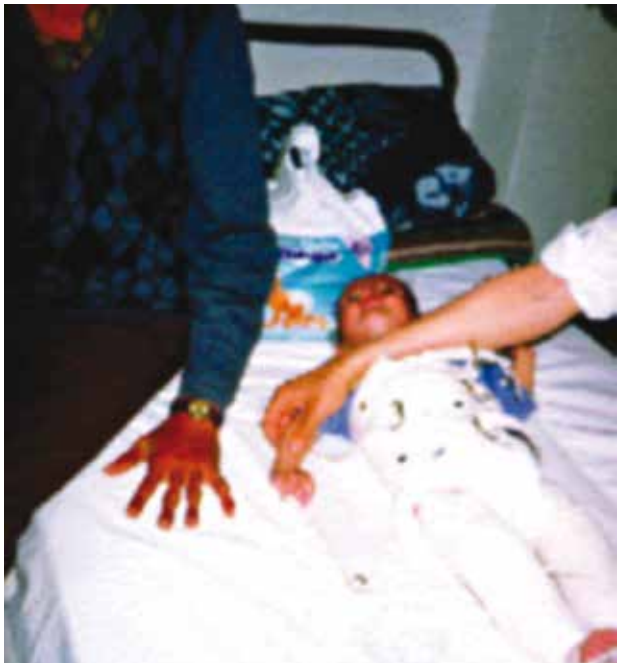

Figure 3: *Dislocations of the hip in a 5-months-old girl manifesting the full clinical criteria of Marfan´s syndrome next to her is her father note the arachnodactyly, this confirms the autosomal dominant pattern of inheritance*

Perilunate dislocations have been reported and are due to excessive carpal ligamentous laxity. Extreme planovalgus deformity of the feet is a common feature. The combination of joint laxity and long digits results in several clinical signs indicative of, but not pathognomonic for, MARFAN´s syndrome. One of these is the "thumb sign", in which the nail of the flexed thumb extends beyond the ulnar border of the clenched fist. This is often referred to as the STEINBERG sign, because STEINBERG recommended that it be used as routine screening for MARFAN´s syndrome. In MARFAN´s syndrome, the vertebral column is significantly affected. Radiographs typically show tall vertebral bodies with elongated transverse processes. The position of the sacrum is low in relation to the iliac crests. The spinal canal may appear widened in the lumbar region, with concavity of the posterior borders of the vertebral bodies. Increased localized kyphosis and evidence of ligamentous instability have been noted in the cervical spine. Scoliosis is common, reported in 30 to 100% of patients. The curve pattern in MARFAN´s syndrome is often double or multiple and pain is a frequent accompaniment. Spondylolisthesis of L4-L5 is relatively common. Many patients have much less florid manifestations; however, the clinician should rely on an awareness of the condition and the strict fulfillment of specific criteria to make the diagnosis. Some patients may have subtle deformities suggestive of the condition, including a taller than average appearance, ligamentous laxity, myopia, and minimal cardiac abnormalities, such as mild mitral valve prolapse. Dilation of the ascending aorta and mitral valve insufficiency are the most common associated cardiovascular anomalies. Ascending aortic dilation may result in aortic valvular incompetence and frequently leads to the formation of a dissecting aortic aneurysm. Aneurysms and dissections may also occur in the descending or thoracolumbar aorta. These cardiovascular anomalies are the most frequent cause of death in patients with MARFAN´s syndrome, and their presence must be carefully sought.

III. GENETICS

MARFAN´s syndrome is transmitted in an autosomal dominant manner. There is great variability in the nature and severity of clinical manifestations, and an unwary physician may not recognize the syndrome in mildly affected patients.

MARFAN´s syndrome is caused by a defective gene FBN1, located on the long arm of chromosome 15. This gene encodes for fibrillin-1, a large glycoprotein closely associated with elastin. In addition to their presence in the aortic media and supensory ligaments of the lens, fibrillin microfibrils are found in skin, tendon, cartilage, and periosteum. In contradistinction, the much rarer Beal´s is caused by a defective gene, FBN2, located on chromosome 5 that encodes for the glycoprotein fibrillin -2.

IV. DIAGNOSIS

Although the defective gene for MARFAN´s syndrome has been identified, the diagnosis remains a clinical one,

based on the fulfillment of diagnostic criteria. Clinicians, particularly primary care physicians and those working in scoliosis clinics, must be alert to the possibility of this condition because the presenting anomaly is most commonly either scoliosis or a heart murmur. The physician should seek a family history of the disorder or its manifestations, especially tall stature, ligament hyperlaxity, poor vision, cardiac anomalies, and sudden or premature death. Consultation should be sought with an ophthalmologist, who should perform a slit-lamp examination to identify the presence of a dislocated lens, and a cardiologist, who should perform echocardiography to assess the diameter of the aortic root and look for evidence of mitral valve prolapse.

V. DIFFERENTIAL DIAGNOSIS

A number of conditions have clinical features suggestive of MARFAN´s syndrome and should be considered in the differential diagnosis. The principal considerations for orthopedic surgeons are homocystinuria, congenital contractual arachnodactyly (BEAL's syndrome), and ophthalmoarthropathy (STICKLER syndrome).

VI. DISCUSSION

Literature review showed that patients with MARFAN´s syndrome might be presented with variable clinical manifestations. A myopathy has occasionally been recorded in patients with MARFAN´s syndrome (5), although poor muscle development is common. In the BEHAN et al., (5) family, a muscle biopsy showed an abnormality in fibrillin immunoreactivity. A dilated aortic root can usually be demonstrated by echocardiography and aortic aneurysms can ensue. ERKULA et al., (15) provide growth charts for individuals with MARFAN syndrome. Some cases have dural ectasia, defined as a ballooning or widening of the dural sac, often associated with herniation of the nerve root sleeves out of the associated foraminae of the spine (3). Patient 1, reported by ADES et al., (2) had major, cranial, dura problems. AHN et al., (3) discusses screening for this condition by MRI and CT scans. Of 32 MARFAN patients, 20 patients were found to have dural ectasia. These patients may have low back pain, headache, proximal leg pain, and weakness and numbness. Dural ectasia occurred in 78% of the cohort examined by SOYLEN et al., (in 3). ADES et al., (1) reported a three-generation family apparently segregating for a form of kyphoscoliosis with some skeletal features of MARFAN syndrome but no heart defects. A mutation in the FBN1 gene (G1796E) was detected.

Dental pulp calcification might be faily frequent in those older than 30 years (8).

De PAEPE et al., (12) discuss the diagnostic criteria. ROSSER et al., (29) compare the "Berlin" and "Ghent" criteria for diagnosis, and stress the importance of looking for dural ectasia in some cases. These ectasia sometimes leak CSF causing postural headache (29). Average life expectancy is halved. 95% of deaths are due to a cardiovascular cause. SHORES et al., (30) studied the effect of beta-adrenergic blockade and concluded that this slowed the rate of aortic dilatation and reduced the development of complications from aortic rupture in some patients with MARFAN syndrome. In British patients, mean age of death was 45.3 years and 50% median cumulative survival was 53 years for males and 72 years for females. There have been about 10 case reports of cerebral aneurysms in MARFAN syndrome, but the association is doubted by some (31). The Committee on Genetics of the American Academy of Pediatrics provide guidelines for management during childhood (13). LIPSCOMB et al., (1997) report the experience of 36 women who had 91 pregnancies. Four had an aortic dissection relating to the pregnancy and two others required aortic surgery following delivery. The incidence of obstetric complications did not exceed expectation.

The condition has been shown to be caused by mutations of the fibrillin-1 gene (FBN1) on chromosome 15. In Scotland, the prevalence is estimated to 1 in 14,000. Twenty-seven percent of cases appeared to be new mutations. Most mutations are unique to individual families. HAYWARD et al., (in 16) screened all 65 exons of the gene and found mutations in 78% of well characterised familial cases but only about 20% of sporadic cases. Intragenic markers can be used for predictive testing (in 6), however care must be taken because of possible genetic heterogeneity. Diagnosis by assessment of fibrillin immunofluorescence on skin biopsies or fibroblast cultures is still technically difficult and the accuracy is not certain. A further family with paternal somatic mosaicism was reported by COLLOD-BÉROUD et al., (11). DIETZ and PYERITZ (14) provide a good review of mutations in the fibrillin gene in MARFAN syndrome. LIU et al., (21) reviewed cases with exon-skipping mutations of the FBN1 gene resulting in a fibrillin-1 chain lacking EGF-like domains. LUI et al., (21) reported a further exon skipping mutation. Many of these cases have the severe neonatal form of the disorder and a dominant negative effect was postulated. PUTNAM et al., (in 6) present data suggesting that cases with mutations in exons 25-27 of the FBN1 gene have relatively severe cardiac manifestations or the neonatal form. COLLOD-BEROUD et al., (11) has published a database of mutations in the FBN1 gene in MARFAN syndrome. LIU et al., (21) reported a 76% detection rate for mutations using denaturing high-performance liquid chromatography. Molecular diagnosis of MARFAN syndrome may be relied on direct analysis of the FBN1 gene at the cDNA level. SCHRIJVER et al., (in 9) provide information on phenotype/genotype correlation in FBN1 mutations and identified 34 cases with premature termination mutations of the FBN1 gene. In this group joint hypermobility was more common but lens dislocation and retinal detachment less common. ROBINSON and GODFREY (28) also provide a good review of FBN1 and FBN2 mutations.

KILPATRICK et al., (1996) reported preimplantation diagnosis of MARFAN syndrome using linked markers. Note that expression can be very variable and there might be an overlap with EHLERS-DANLOS - kyphoscoliotic type. Molecular studies might be needed to sort this out.

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