Republic of Iraq

Ministry of higher education and scientific research

University of Diyala

College of Medicine

Department of Histology

Marfan Syndrome

Presented by:

Ahmed Sami Majeed

Supervised by:

Ass.Lec: Hala Yassin Kadhim

2020-2021

Abstract

Marfans syndrome is an autosomal dominant condition with an envisioned prevalence of 1 in 10,000 to 20,000 individuals. This rare hereditary connective tissue disease impacts many components of the body. The prognosis of Marfans syndrome is established according with a evaluation of the diagnostic criteria, known as the ghent nosology, via a comprehensive evaluation in large part primarily based totally on a mixture of most important and minor scientific manifestations in diverse organ structures and the own circle of relatives history. Aortic root dilation and mitral valve prolapse are the principle displays amongst the cardiovascular malformations of Marfans syndrome. The

pathogenesis of Marfans syndrome has not been absolutely elucidated. However, fibrillin-1 gene mutations are believed to exert a dominant bad effect, Marfans syndrome is termed a fibrillinopathy, together with different connective tissue problems with diffused differences in clinical manifestations. The treatment may include prophylactic β-blockers and angiotensin II-receptor blockers so as to gradual down the dilation of the ascending aorta, and prophylactic aortic surgery, β-blocker therapy might lessen TGF-β activation, which has been diagnosed as a contributory factor in Marfans syndrome.

Introduction

Marfan syndrome (MFS) is an autosomal dominant disorder of connective tissue with a prevalence of one per 5000 individuals.[1] The disease is mainly caused by mutations of the fibrillin-1 (*FBN1*) gene encoding for extracellular matrix protein fibrillin-1. MFS patients present with several symptoms, including aortic dilation and ectopia lentis MFS has been named to Professor Antoine-Bernard Marfan. In the Bulletin of the Medical Society of Paris in 1896, Professor Marfan described a 5.5-year-old girl with long slender digits and other skeletal abnormalities.Nowadays, experts agree that the child was probably affected by 'contractural arachnodactyly', a disorder of connective tissue caused by *FBN2* mutations.

Epidemiology

Marfan syndrome happens in 1 to twoin line with 10,000 people and impacts males and girls equally.[4] Clinical manifestations generally tend to become extra obvious with growing age. In data stated earlier than 1972, the existence expectancy of sufferers with this syndrome was decrease than that for the overall population, however prophylactic treatment of aortic valve and root disease has ended in a almost regular existence expectancy.[5] Most instances result from mutations in genes encoding for fibrillin-1.[3,6,7] The fibrillin-1 gene, *FBN1*, is positioned on chromosome 15.[6]*FBN1* mutations are present in >90% of patients with Marfan syndrome.[8]*FBN1* mutations were shown to growth the susceptibility of fibrillin-1 to proteolysis in vitro, main to fragmentation of microfibrils.[6] In addition, fibrillin mutations might also additionally cause modifications in mobileular-to-mobileular signaling thru latent binding switch protein. Other manifestations are because of different consequences of the fibrillin mutations. familial ectopia lentis, ,

extracellular matrix formation, mobileular-cycle arrest, and apoptosis.[7] it now seems that dysfunctional TGF-β signaling because of fibrillin mutations might also additionally play a extra outstanding function in the path-physiology of Marfan syndrome.[9] In addition, multiplied TGF-β activation and signaling secondary to mutations in the *TGFBR1* gene on chromosome nine and the *TGFBR2* gene on chromosome three were recognized in groups of patients with Marfan syndrome or Marfan-associated disorders.[7,10]

PATHOPHYSIOLOGY:

Fibrillin-1 and the intently related fibrillin-2 protein are principal additives of the 10 nm microfibrils of the extracellular matrix. These fibrillins are extracellular glycol-proteins comprised in particular of tandemly repeated epidermal increase factor (EGF)-like modules, maximum of which satisfy the consensus for calcium binding (cbEGF-like motifs). Both proteins make a contribution to unique bodily residences of elastic and non-elastic tissues. Recent studies has challenged classical pathogenetic ideas of Marfan syndrome

Etiology

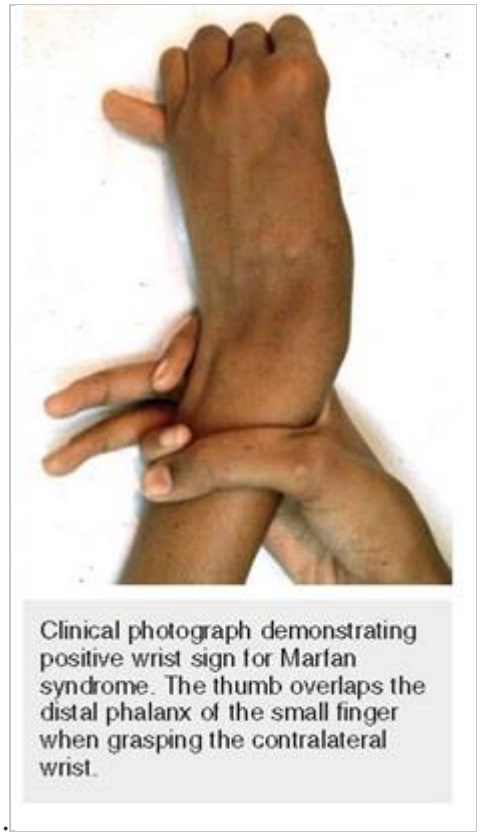
In the vast majority of cases, Marfan syndrome is caused by mutations of the *FBN1* gene(15q21) which codes for fibrilline-1,a protein essential connective tissues. Frontier forms have been identified that are secondary to mutations in the *TGFBR2* gene located on chromosome 3, which codes for a TGF-beta receptor.

Differential diagnosis

Differential diagnoses include MASS syndrome, Shprintzen-Goldberg syndrome, mitral valve prolapse, Ehlers-Danlos syndrome and other diseases that present with aortic aneurysm such as Loeys-Dietz syndrome (see these terms).

General Diagnosis

Suspicion for Marfan syndrome is raised by the presence of its cardinal manifestations, including tall stature, skinny habitus, long narrow limbs (ie, dolichostenomelia), arachnodactyly, pectus deformity, and scoliosis. ligamentous laxity, and camptodactyly. The thumb signal is high quality while the complete nail of the thumb over the ulnar border of the hand while the thumb is clenched with out assistance



Clinical photograph demonstrating positive wrist sign for Marfan syndrome. The thumb overlaps the distal phalanx of the small finger when grasping the contralateral wrist.

Clinical image demonstrating fantastic wrist signal for Marfan syndrome. The thumb overlaps the distal phalanx of the small finger when grasping the contralateral wrist

Critical Diagnosis

is important to beginning suitable prophylactic scientific and surgical treatment and preventing deadly aortic dissection. Diagnosis is guided with the aid of using the Ghent nosology[11]. The Ghent nosology turned into evolved as an development tat the Berlin diagnostic criteria of 1986,[12] which did not certainly distinguish people with Marfan syndrome from people with mild connective tissue phenotypes or people with versions of everyday anatomy. Included the Ghent nosology are greater stringent necessities for prognosis in loved ones of an affected individual, capability contribution of molecular analysis, and delineation of preliminary standards for prognosis of different heritable situations with

in part overlapping phenotypes.[11]

The Ghent Nosology for the Diagnosis of Marfan Syndrome

System	Major Criteria	Minor Criteria
Skeletal*	Presence of at least four of the following: Pectus carinatum Pectus excavatum requiring surgery Reduced upper-to-lower segment ratio or arm span–to-height ratio >1.05 Positive wrist and thumb signs Scoliosis >20° or spondylolisthesis Reduced extension at the elbows (<170°) Medial displacement of the medial malleolus causing pes planus Protrusio acetabuli	Pectus excavatum of moderate severity Joint hypermobility Highly arched palate with crowding of teeth Facial appearance: dolichocephaly, malar hypoplasia, enophthalmos, retrognathia, down-slanting palpebral fissures
Ocular†	Ectopia lentis (requires slit lamp examination)	Abnormally flat cornea (as measured by keratometry) Increased axial length of globe (as measured by ultrasonography) Hypoplastic iris or hypoplastic ciliary muscle causing decreased miosis
Cardiovascular‡	Dilatation of the ascending aorta with or without aortic regurgitation and involving at least the sinuses of Valsalva Dissection of the ascending aorta	Mitral valve prolapse with or without mitral valve regurgitation Dilatation of the main pulmonary artery, in the absence of valvular or peripheral pulmonic stenosis or any other obvious cause (patient aged <40 years) Calcification of the mitral anulus (patient aged <40 years) Dilatation or dissection of the descending thoracic or abdominal aorta (patient aged <50 years)
Pulmonary§	None	Spontaneous pneumothorax Apical blebs
Skin and integument‖	None	Stretch marks not associated with marked weight changes, pregnancy, or repetitive stress (typically located on the shoulders, back, and thighs) Recurrent or incisional hernia
Dura¶	Lumbosacral dural ectasia evident on CT or MRI	None
Family history#	Having a parent, child, or sibling who meets these diagnostic criteria independently Presence of a mutation in *FBN1* known to cause Marfan syndrome Presence of a haplotype around *FBN1*, inherited by descent, known to be associated with unequivocally diagnosed Marfan syndrome in the family	None

* For the skeletal system to be considered involved, at least two major criteria or one major criterion plus two minor criteria must be met.
† For the ocular system to be involved, at least two minor criteria must be met.
‡ For the cardiovascular system to be involved, one major criterion or one minor criterion must be met.
§ For the pulmonary system to be involved, one minor criterion must be met.
‖ For the skin and integument to be involved, one minor criterion must be met.
¶ For the dura to be involved, one major criterion must be met.
# For the family/genetic history to be contributory, one major criterion must be met.
Adapted with permission from De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE: Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996;62:417-426.

The Ghent Nosology for the Diagnosis of Marfan Syndrome

Because of the age dependence of many Marfan capabilities, the Ghent nosology does now no longer exclude Marfan syndrome in children.[9]

Under the Ghent nosology, medical capabilities of 7structures are assessed to decide whether important standards and system involvement are present. Prognosis calls for the presence of important standards in as a minimum two exclusive organ structures and involvement of a 3rd organ system.[11] prognosis calls for assembly a first-rate criterion in the family records and one important criterion in an organ system, and involvement of a 2d organ system[11]

Family records is now not used continually high-quality; about 25% of instances are the end resultof latest mutations.[13,14] and >a hundred thirty five mutations in the fibrillin gene were identified.[8] In addition, fibrillin-1 mutations may motive different, Marfan-like disorders. Finally, 9% to 34% of affected patients have no identifiable fibrillin-1 mutations.[8] Currently, molecular prognosis lacks sensitivity and

specificity and is neither efficient nor beneficial in all instances.[8,10] The incapacity to locate a mutation in *FBN1* or molecular abnormality in fibrillin-1 does now no longer exclude the prognosis. Mutation evaluation is first-rate used to decide whether or not a pre-symptomatic individual has inherited a described phenotype visible in the family.[9] findings of Marfan syndrome aren't present, and the diagnostic standards for Marfan syndrome are now no longer met.[15]

Diagnosis

can be difficult, especially in children, and follow-up is needed to differentiate this entity from Marfan syndrome. **Loeys-Dietz** syndrome is similar to Marfan syndrome in its affiliation with scoliosis, pectus deformity, and aortic root aneurysms.[16] However, in contrast to Marfan syndrome, Loeys-Dietz syndrome is additionallyrelated to hypertelorism, cleft palate, clubfoot, Chiari I malformation, and clean bruising. The aortic aneurysms in patients with Loeys-Dietz syndrome dissect at youngera while and small sizes; thus, surgical treatment in such patients is indicated for smaller lesions than in patients with Marfan syndrome.[16] Loeys-Dietz syndrome is inducedwith the aid of using mutations in TGF receptors 1 and 2, which bring about extended TGF-β signaling.

Manifestations;

Cardiovascular

The aorta in patient Marfan syndrome may also go through cystic medial degeneration, which is characterized through fragmented elastic fibers, a lower in smooth muscle cells, and the deposition of collagen and mucopoly-saccharides among cells of the media.[9] Risk factors for aortic dissection consist of diameter of the sinus of Valsalva >five cm, extensive aortic dilatation, dilatation charge of >1.five mm consistent with year, and a positive own circle of relatives history.[17] Aortic valve insufficiency may also also occur.. In a randomized potential trial, Shores et al[18] confirmed that β-blockers and angiotens inconverting enzyme-inhibitor medicinal drug test be prescribed.
Surgical restore of aortic root aneurysms has stepped forward the lifestyles expectancy in persons with Marfan syndrome from thirds of ordinary to almostordinary.[5,13] Prophylactic aortic root surgical operation is taken into consideration whilst the aortic diameter on the sinus of Valsalva is >five cm.[11,17] Earlier surgical operation can been courage

whilst the foundation is hastily enlarging or with own circle of relatives records of dissection. The effects of prophylactic aortic root surgical operation are advanced to the ones of emergent surgical operation.[19]

Surgery for aortic aneurysm

The rate of acute aortic dissection is directly proportional to the maximum diameter of the aorta. Elective surgery to repair the aortic root is recommended when the maximum aortic diameter reaches 5 cm. Additional considerations include the rate of aortic growth and family history of aortic dissection at a size less than 5 cm. Earlier surgical intervention is recommended for individuals with an increase in aortic diameter exceeding 1 cm per year.

Ocular;

Ocular manifestations consist of ectopia lentis, myopia, glaucoma, cataracts, and retinal detachment. Ectopia lentis is found in approximately 60% of affected persons.[20,21] This circumstance takes place in utero and for that reason may be identified at the first ophthalmologic examination. Annual ophthalmologic follow-up is required to understand the improvement of different manifestations.

Musculoskeletal Overgrowth;

Disproportionate boom of the lengthy bones is frequently the maximum apparent manifestation of Marfan syndrome. Overgrowth may be quantified with the aid of using an arm span length >1.05 times peak or a discounted upper-to-decrease section ratio. Arachnodactyly in combination with free joints effects with inside the wrist and thumb signs defined previously

Scoliosis

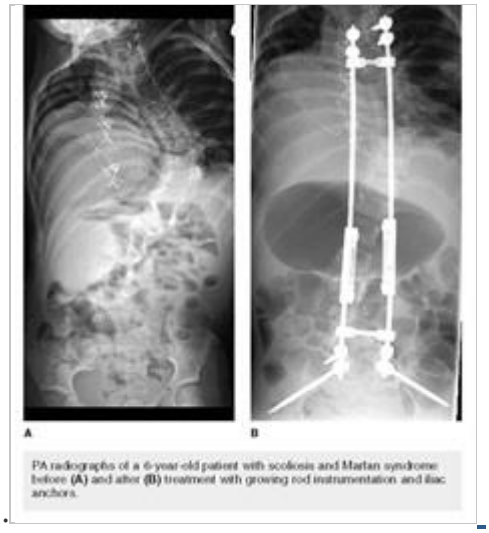
Scoliosis is present in 60% of patients with Marfan syndrome[22] The curves resemble the ones of idiopathic scoliosis, how ever there's a better incidence of double thoracic and triple foremost curves.[23] The sagittal profile varies widely. Alignments encompass hypokyphosis, hyperkyphosis, and thoracolumbar kyphosis with thoracic lordosis; 40% of patients have kyphosis >50°.[24] In a evaluation of spinal deformity in

patients with Marfan syndrome, Sponseller et al[24] observed that development of scoliosis took place beyond skeletal adulthood in patients with curves >40° and will bring about deformity, breathing deficits, and returned pain. In addition, the authors observed that curve development can be quicker in such patients than in patients with idiopathic scoliosis due to the fact curves >50° development at an average fee of 3° ± 4° consistent with12 months in adulthood.[24]

Clinical photograph of a patient with scoliosis associated with Marfan syndrome;

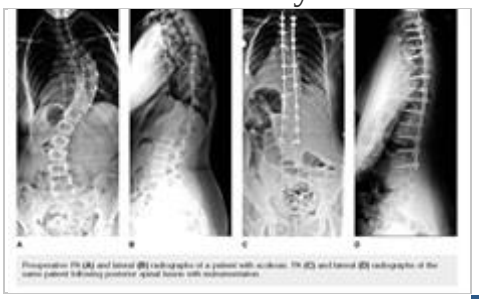
Characteristic vertebral anomalies also are observed in those patients. Osseous abnormalities encompass slim pedicles, extensive transverse processes, and vertebral scalloping.[24]

Most curves are of small value and do now no longer require remedy. Treatment of large curves can be challenging. Nonsurgical remedy of scoliosis in patients with Marfan syndrome is much less hit than in people with idiopathic scoliosis. Sponseller et al[23] evaluated bracing in patients with Marfan syndrome, curve ≤45°, Risser signal of grade zeroto two at the starting of bracing, and endorsed brace wear ≥18 hours in keeping with day. Success was described as curve progression ≤5° and a very last curve ≤45°. Treatment was a hit in fourof twenty-two sufferers who finished brace wear.[23] Bracing is currently indicated for developing kids with Marfan syndrome and curves of 15° to 25° and is an alternative for curves among 25° and 45° Surgery is taken into consideration for sufferers with curves >45°. In young patients developing rod instrumentation can be necessary. Iliac fixation can be useful in a few cases[25]



PA radiographs of a 6-year-old patient with scoliosis and Marfan syndrome before (A) and after (B) treatment with growing rod instrumentation and iliac anchors.

PA radiographs of a 6-year-vintagepatient with scoliosis and Marfan syndrome.
In a retrospective assessment of patients with Marfan syndrome receiving surgical correction for spinal deformity, Jones et al[26] observed that the variety of surgical headaches related to spinal fusion becom better in patients with Marfan syndrome than within side the regular population. Failure of fixation is a not unusual place hassle in sufferers with Marfan syndrome due to the skinny laminae, skinny pedicles, and osteopenia. Because of those properties, Jones et al[26] recommended that the variety of fixation factors have to be maximized. Pedicle screws are preferred, and suitable pedicles may be recognized with preoperative CT scan.[27] Sublaminar wires have to be tightened slowly, and rod compression and distraction have to be done gradually. [26] .
the improvement of scoliosis or kyphosis at top or decrease fusion ranges—may arise after surgery. Jones et. The choice of the arthrodesis ranges is critical; care want to be taken to consist of all important and structural curves and hold away from fusing too brief a segment [25] To lower the hazard of including on, Jones et al[26] counseled that any curve >30° must be blanketed in the arthrodesis. Selective thoracic arthrodesis for double curves would possibly not be successful. Arthrodesis of all vertebrae the Cobb attitude and extension to the sagittal strong area is recommended.[26] However, despite suitable choice of ranges, including on can also additionally nevertheless arise.[26]



Preoperative PA (A) and lateral (B)radiographs of a affected person with scoliosis
The weaker connective tissue found in people with Marfan syndrome might also additionally make a contribution to this complication.[26] Jones et al[26] suggested proscribing dissection to the quantity wanted for instrumentation and fusion, specially minimizing dissection of the interspinous ligaments. Patients in the collection with curve decomposition exhibited excessive postoperative correction percentages, suggesting that intense curve correction might also additionally bring about curve decomposition. Preoperative assessment need to additionally cope with the threat of aortic dissection and the want for anticoagulation in the patient with prosthetic valves. Clotting parameters need to additionally be checked.

Dural Ectasia;

Dural ectasia, an enlargement of the outer layer of the dural sac and nerve root sleeves, is described with the aid of using growth of the neural canal everywhere alongside the spinal column, thinning of the cortex of the pedicles or laminae, widening of the neural foraminae, or an anterior meningocele.[11] Dural ectasia, maximum of ten positioned among L5 and S2, is not unusual happen in people with Marfan syndrome; it's far found in as much as 95% of affected patients as recognized with the aid of using MRI[28,29] In many cases, dural ectasia

T2-weighted axial MRI scan demonstrating dural ectasia.

is related to lower back pain.[30] .
T2-weighted axial MRI test demonstrating dural ectasia.
Definitions of dural ectasia vary, Morphologic standards consist of bulging of the dural sac, loss of epidural fatson the posterior wall of the vertebral body, and the presence of radicular cysts.[31] Ahn et al[32]

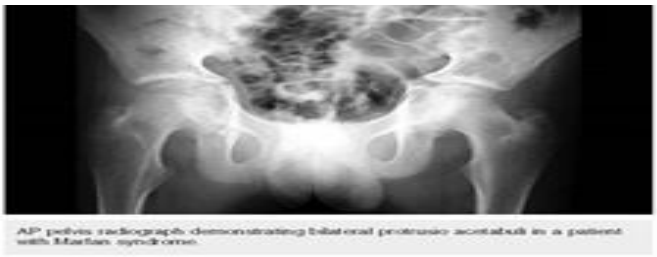
Cervical Spine Abnormalities

The cervical spine on occasion demonstrates abnormalities in patients with Marfan syndrome. Hobbs et al[33] reviewed 104 patients with Marfan syndrome; 16% had focal kyphosis and 54% had improved atlanto axial translation. An improved incidence of radiographic basilar impression (36%) became partially associated with improved odontoid height. Cervical stenosis is rare,[33] as is multilevel cervical subluxation.[34]

Protrusio Acetabuli;

Protrusio acetabuli is the protrusion of the medial wall of the acetabulum into the pelvic cavity. The incidence in Marfan syndrome is 27 according

to the middle-aspect-attitude criterion of >50% and 16 according to the acetabular-ilioischial distance criterion of ≥three mm in adult males and ≥6 mm in females.[35] Affected people are asymptomatic till hip osteoarthritis develops, >1 mm in boys, ≥6 mm in women, and >three mm in girls; and crossing of the iliopectineal line via way of means of the acetabular line[36]



AP pelvis radiograph demonstrating bilateral protrusio acetabuli in a patient with Marfan syndrome.

For patients elderly eight to 10 years with development of protrusio, Steel[37] radiographic indices of acetabular intensity generally tendto stay strong after age 20 years.[35] in patients with out protrusio ($P < 0$>[35]When protrusio does bring about symptomatic osteoarthritis in older sufferers, overall hip arthroplasty can be performed. Nonstructural bone grafting of the medial hollow space is regularly required.[36] Patients elderly<40>[36]

Respiratory System

Pectus excavatum is found in up to 2 thirds of children with Marfan syndrome.[41] A restrictive ventilatory scan also additionally occur, although surgical treatment generally is executed for cosmoses and now no longer for respiration function. Because this situation can recur postoperatively in children, surgical intervention need to be not on currently possible. Spontaneous pneumothorax came about in 4.4% of patients with Marfan syndrome aged >12 years in a single series.[42] Recurrence of pneumothorax is common.

Prognosis

Advances in the management of the cardiovascular manifestations of MFS have led to a significant decrease in the morbidity and mortality that are associated with this condition. Before the advent of pharmacologic and surgical therapy for aortic root and valvular disease, the life expectancy for patients with MFS was about two thirds that of the healthy population. Aortic dissection and congestive heart failure due to aortic and mitral valvular anomalies accounted for over 90% of the known causes of death.

Patient longevity now approaches that of persons without MFS.

Treatment

depends on which parts of the body are affected. An aortic aneurysm may be treated with medicine or medicine plus surgery. Medicine is used to lower blood pressure to help prevent an aneurysm from rupturing and causing a dissection of the aorta.[2]
Severe scoliosis and breastbone problems may require surgery. Eye conditions may also require surgery.

Conclusion

Our patients management shows the need of a multidisciplinary technique with early visible entity, prognosis, and referral of MFS patients in number one care. The Ghent diagnostic standards useful resource with the prognosis via way of means of scoring the pleiotropic outcomes of the *FBN1* mutations on the six organ structures laid low with MFS. The early identity and referral to the heart specialist might also additionally have doubled the existence span of our affected person via way of means of stopping a deadly aortic aneurysm/dissection. As the number one care providers, we maintain to coordinate the multidisciplinary care with ongoing follow-up with the heart specialist, ophthalmologist, orthopedist, and genetic counselor as the adolescent tactics maturity and considers having organic children.

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Disscusion

Marfan syndrome merits specific interest through number one care physicians for 2 reasons. First, number one care is taken into consideration a patient's first portal of access into the fitness care gadget. Second, there are useful scientific clues that make it a screen able circumstance for number one care physicians. The Ghent standards constitute the same old for diagnosing Marfan syndrome according with scientific symptoms and symptoms and own circle of relatives records.3–four They employs a fixed of principal and minor manifestations in sever a tissues, which include the skeletal, ocular, cardiovascular, and pulmonary systems, and the dura, pores and skin and integument.

Diagnosis is made if principal standards are recognized in as a minimum special organ systems, and if there's involvement of a 3rd organ gadget with both a prime or minor manifestation. If a own circle of relatives records of Marfan syndrome is fantastic then involvement of best organ systems, which include one principal criterion, is essential for diagnosis.

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