Pediatric Education and Research
Volume 1 Number 1, January - March 2013

Marfan's Syndrome

Sunil Mhaske[1], Ramesh B. Kothari[2], Sandeep Deokate[3], Ram Sethi[4], Pavan Suryawanshi[5], Nishad Patil[6], Rahul Maski[7], Nivrutti Mundhe[8], Subhash Yadav Bhosale[9]

[1]Professor & Head Dept of Paediatrics, [2]Assistant Professor; [3]Residents, [4]Residents, [5]Residents, [6]Residents, [7]Residents, [8]Residents, [9]Intern, Padmashree Dr. Vithalrao Vikhe Patil Medical College & Hospital, Near Govt. Milk Dairy, Vilad Ghat, Ahmednagar – 414111

Abstract

Marfan's syndrome is a genetic disorder of the connective tissue. People with Marfan's tend to be unusually tall, with long limbs and long, thin fingers. The syndrome is inherited as a autosomal dominant trait, carried by the gene FBN1, which encodes the connective protein fibrillin-1.

Key words: Marfan's syndrome; Connective tissue disorder; FBN1; Fibrillin-1.

Introduction

Marfan's syndrome is an inherited connective tissue disorder that is transmitted as an autosomal dominant trait. People have a pair of FBN1 genes. Because it is dominant, people who have inherited one affected FBN1 gene from either parent will have Marfan's syndrome. Hence, one affected parent is sufficient to pass on the disorder to the child. Being a connective tissue disorder, Marfan's syndrome affects almost all of the body's systems, including the skeletal, cardiovascular, nervous, skin, and pulmonary systems.

Case summary

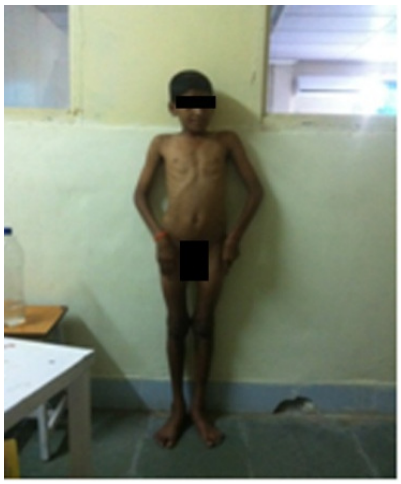
Eleven years boy brought by his parents to our OPD with complaints of diminishing of vision since birth. There was no history of trauma to eyes. Also he was not a known case of juvenile diabetes mellitus or juvenile hypertension. There was no history of any other eye complaint, delayed milestones, any surgery, respiratory illness, cardiac illness. In family history, his father was also suffering from similar complaints along with some cardiac problem and long limb deformities, details of which were not available. His father died 6 years ago in same course of illness. Also his paternal grandmother was suffering from similar illness & she expired in same course. His parents had family history of non-consanguineous marriage. He was a full term normal hospital delivery with good cry and adequate weight at birth. Our case was first issue of parents out of their 3 siblings (2 males & a female); none of them having any congenital anomaly or similar illness. We admitted the boy to our hospital in paediatric ward for further investigations & management.

On examination, his vital parameters were normal as per his age. In anthropometric examination, he was having extra long upper limbs & lower limbs. His head circumference was 52 cm, chest circumference – 59 cm, height – 140cm, upper segment /lower segment ratio – 0.70 (reduced), arm span –

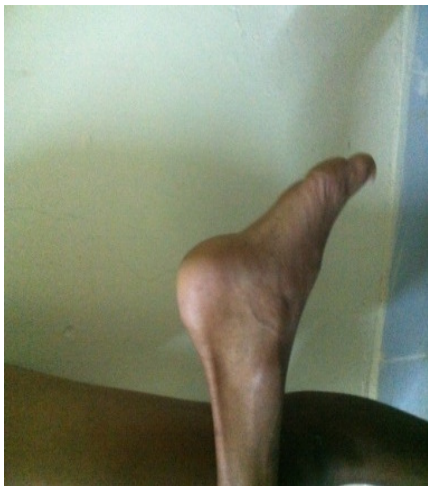
Corresponding Author: Dr. Sunil Mhaske, Professor & Head Dept of Paediatrics, Padmashree Dr. Vithalrao Vikhe Patil Medical College & Hospital, Near Govt. Milk Dairy, Vilad Ghat, Ahmednagar – 414111. E-mail: sunilmhaske@rocketmail.com, Mobile No: +917588024773.

(Received on 15.01.2013, Accepted on 04.02.2013)

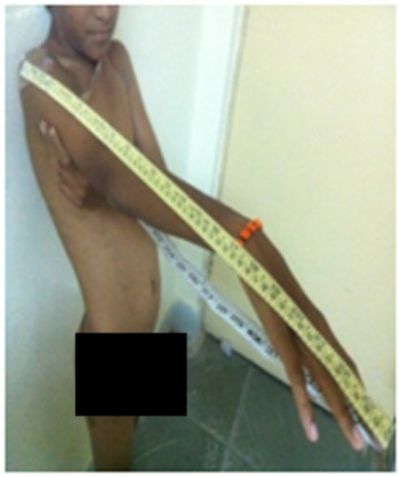
Reduced elbow extension



Hind-foot deformity

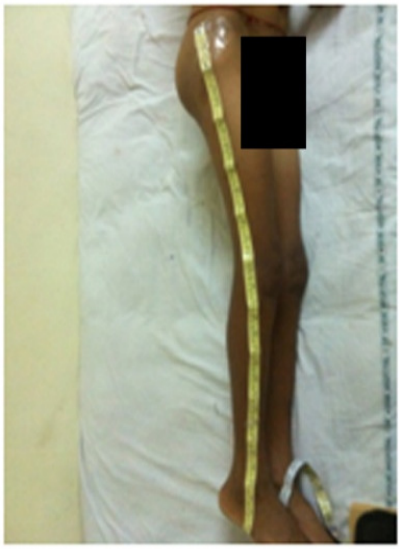


Long upper limb



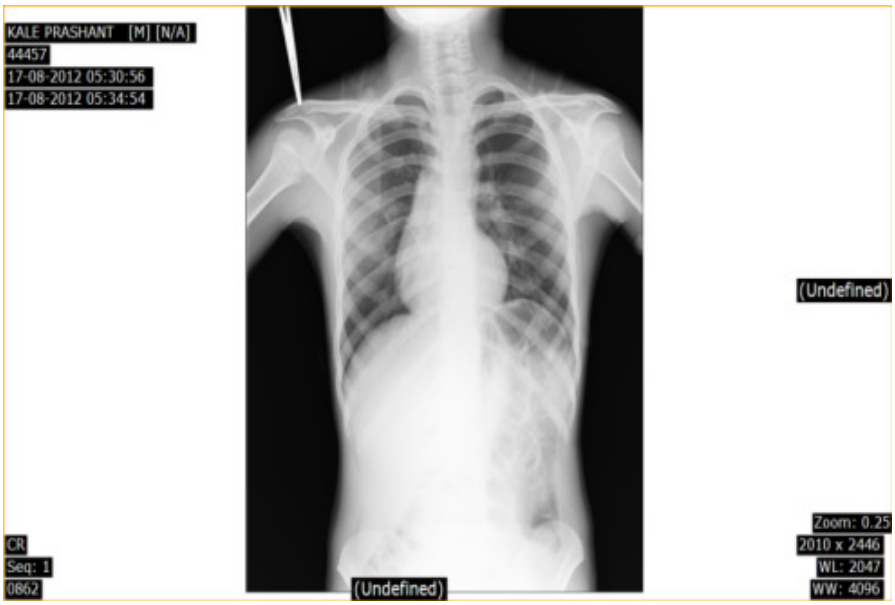
Thumb sign

Long lower limb

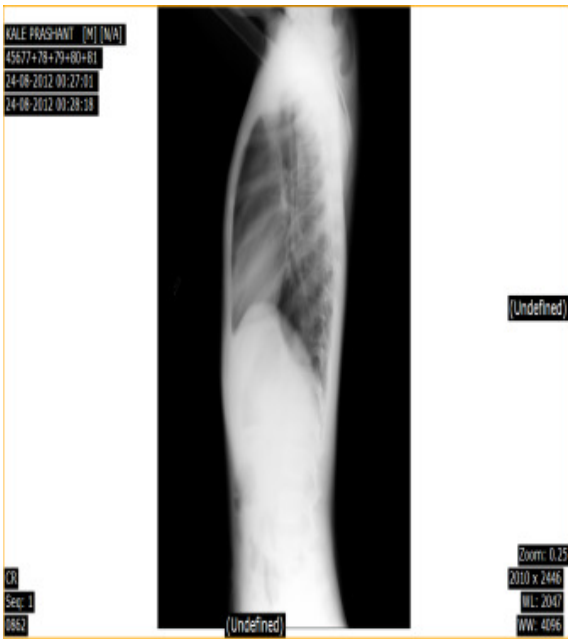


Wrist sign

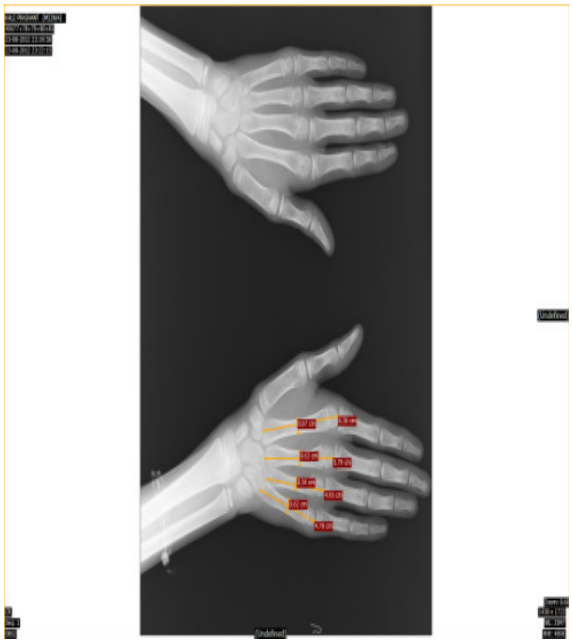
Chest x-ray PA view



Chest x-ray lateral view



X-ray showing long metacarpals

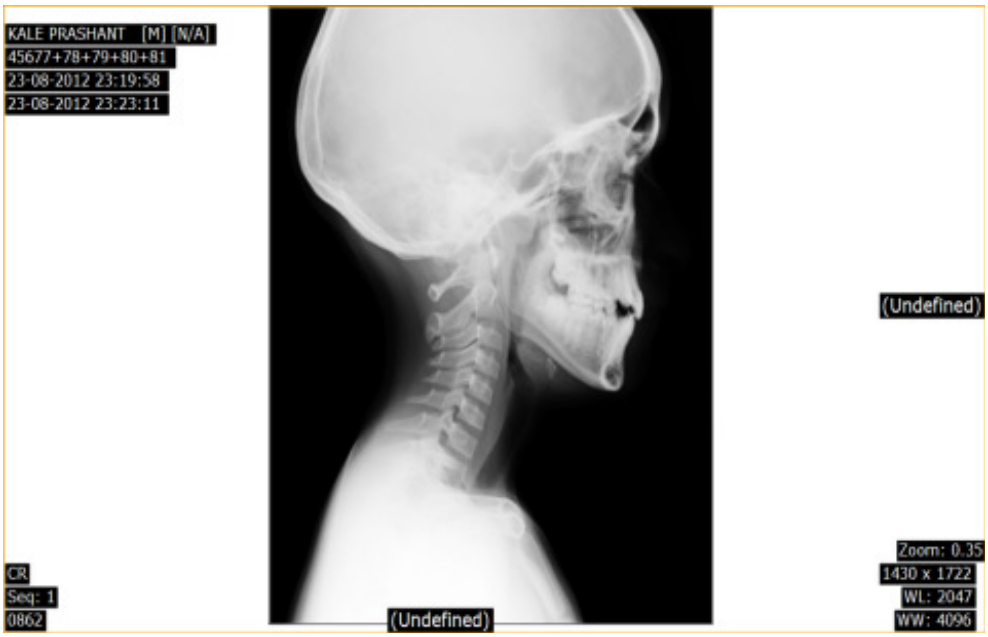


142cm, mid arm circumference – 16 cm & weight – 25.03 kg. All systemic examinations were within normal limits. Opinion from Ophthalmologist was taken which after fundoscopy stated that his vision was 6/36 for both the eyes & there was superotemporal displacement of lenses in both the eyes. No retinal detachment was there. There was no any spine deformity like scoliosis or chest deformity present.

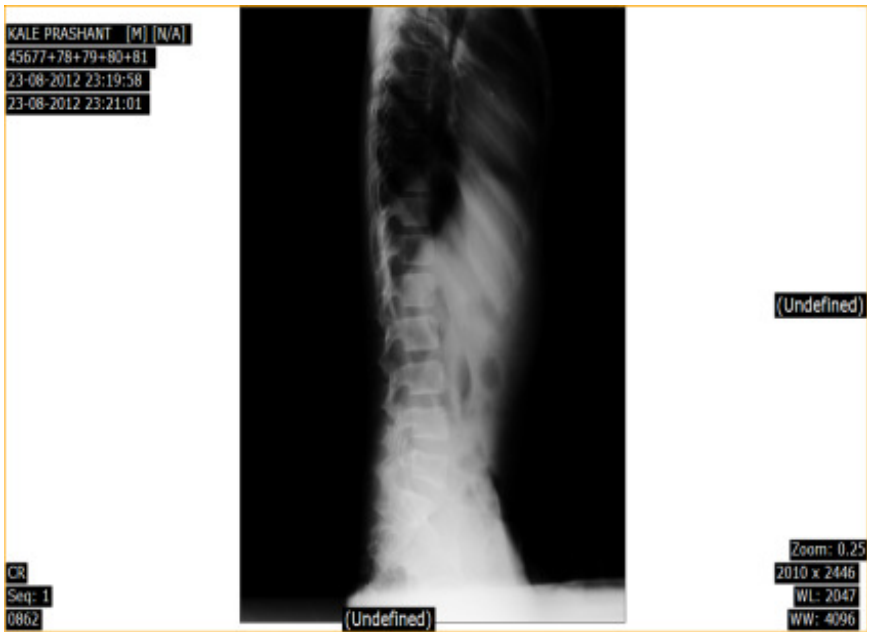
The following investigations were done:

Hb – 10.5 gm%; TLC – 6900/cmm; (N– 46, L – 42, E – 07, M – 05.)

X-ray skull



X-ray Spine



Serum electrolytes:

Sodium – 138 mmol/L. Potassium – 4.4 mmol/L. Calcium – 9.8 mg%.

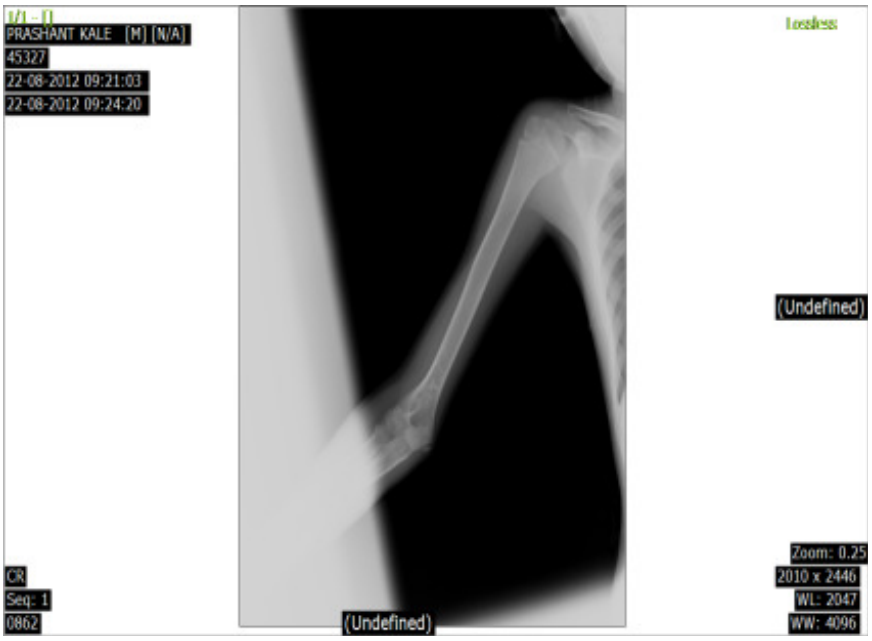
Urine examination was normal.

X-ray chest was normal.

2D ECHO didn't show any cardiac anomaly.

Colour Doppler of aorta didn't reveal any abnormality.

X-ray long bone (right arm)



We diagnosed this as Marfan's syndrome on following basis:

- Family history of Marfan's syndrome was present.
- Superotemporal displacement of lens.
- Systemic Score: Total = 8.
  - Wrist and thumb sign = 3
  - Hind-foot deformity = 2
  - Reduced elbow extension = 1
  - Myopia >3 diopters = 1
  - Reduced upper segment/lower segment ratio & increased arm/height & no severe scoliosis = 1

Discussion

Marfan's syndrome is a genetic disorder of the connective tissue with autosomal dominant inheritance. People with Marfan's tend to be unusually tall, with long limbs and long, thin fingers. Marfan's syndrome is named after Antoine Marfan, the French paediatrician who first described the condition in 1896. The gene linked to the disease was first identified by Francesco Ramirez in 1991.

Marfan's syndrome has a range of expressions, from mild to severe. The most serious complications are defects of the heart valves and aorta. It may also affect the lungs, the eyes, the dural sac surrounding the spinal cord, the skeleton and the hard palate.

Marfan's syndrome affects males and females equally, and the mutation shows no ethnic or geographical bias. Estimates indicate about one in 3,000 to 5,000 individuals have Marfan's syndrome.

Signs and Symptoms

The constellation of long limbs, dislocated lenses and the aortic root dilation are generally sufficient to make the diagnosis of Marfan's syndrome with reasonable confidence.

Skeletal System

Most of the readily visible signs are associated with the skeletal system. Many individuals with Marfan's syndrome grow to above-average height. Some have long, slender limbs (dolichostenomelia) with long fingers and toes (arachnodactyly). An individual's arms may be disproportionately long, with thin, weak wrists. In addition to affecting height and limb proportions, Marfan's

syndrome can produce other skeletal anomalies. Abnormal curvature of the spine (scoliosis), abnormal indentation (pectus excavatum) or protrusion (pectus carinatum) of the sternum are not uncommon. Other signs include abnormal joint flexibility, a high palate, malocclusions, flat feet, hammer toes, stooped shoulders, and unexplained stretch marks on the skin. It can also cause pain in the joints, bones and muscles in some patients.

Eyes

Marfan's syndrome can also seriously affect the eyes and vision. Nearsightedness and astigmatism are common, but farsightedness can also result. Subluxation (dislocation) of the crystalline lens in one or both eyes (ectopia lentis) also occurs in 80% of patients. In Marfan's syndrome, the dislocation is typically superotemporal whereas in the similar condition homocystinuria, the dislocation is inferonasal. Sometimes eye problems appear only after the weakening of connective tissue has caused detachment of the retina. Early

Lens dislocation in Marfan's syndrome;

The lens was kidney-shaped and was resting against the ciliary body

onset glaucoma can be another related problem.

Cardiovascular System

The most serious signs and symptoms associated with Marfan's syndrome involve the cardiovascular system: undue fatigue, shortness of breath, heart palpitations, racing heartbeats, or angina pectoris. Cold arms, hands and feet can also be linked to Marfan's syndrome because of inadequate circulation. A heart murmur, abnormal reading on an ECG, or symptoms of angina can indicate further investigation. The signs of regurgitation from prolapse of the mitral or aortic valves result from cystic medial degeneration of the valves, which is commonly associated with Marfan's syndrome. However, the major sign that would lead a doctor to consider an underlying condition is a dilated aorta or an aortic aneurysm. Sometimes, no heart problems are apparent until the weakening of the connective tissue (cystic medial degeneration) in the ascending aorta causes an aortic aneurysm or aortic dissection, a surgical emergency. An aortic dissection is most often fatal and presents with pain radiating down the back, giving a tearing sensation.

Lungs

Marfan's syndrome is a risk factor for spontaneous pneumothorax. In spontaneous unilateral pneumothorax, air escapes from a lung and occupies the pleural space between the chest wall and a lung. The lung becomes partially compressed or collapsed. This can cause pain, shortness of breath, cyanosis, and, if not treated, it can cause death.

Central Nervous System

Dural ectasia, the weakening of the connective tissue of the dural sac encasing the spinal cord, though not life-threatening, can reduce the quality of life for an individual. It can be present for a long time without producing any noticeable symptoms. Symptoms that can occur are lower back pain, leg pain, abdominal pain, other neurological symptoms in the lower extremities, or headaches. Such symptoms usually diminish when the individual lies flat on his or her back. Other spinal issues associated with Marfan's syndrome include degenerative disk disease, spinal cysts and dysautonomia.

Pathogenesis

Marfan's syndrome is caused by mutations in the *FBN1* gene on chromosome 15, which encodes the glycoprotein fibrillin-1, a component of the extracellular matrix. Fibrillin-1 protein is essential for the proper formation of the extracellular matrix, including the biogenesis and maintenance of elastic fibers. The extracellular matrix is critical for both the structural integrity of connective tissue, but also serves as a reservoir for growth factors. Elastin fibers are found throughout the body, but are particularly abundant in the aorta, ligaments and the ciliary zonules of the eye; consequently, these areas are among the worst affected.

Transforming growth factor beta (TGFâ) plays an important role in Marfan's syndrome. Fibrillin-1 directly binds a latent form of TGFâ, keeping it sequestered and unable to exert its biological activity. The simplest model of Marfan's syndrome suggests reduced levels of fibrillin-1 allow TGFâ levels to rise due to inadequate sequestration. Although it is not proven how elevated TGFâ levels are responsible for the specific pathology seen with the disease, an inflammatory reaction releasing proteases that slowly degrade the elastin fibers and other components of the extracellular matrix is known to occur. The importance of the TGFâ pathway was confirmed with the discovery of the similar Loeys-Dietz syndrome involving the *TGFâR2* gene on chromosome 3, a receptor protein of TGFâ. Marfan's syndrome has often been confused with Loeys-Dietz syndrome, because of the considerable clinical overlap between the two pathologies.

Diagnosis

Diagnostic criteria of Marfan's syndrome were agreed upon internationally in 1996. A diagnosis of Marfan's syndrome is based on family history and a combination of major and minor indicators of the disorder, for example: four skeletal signs with one or more signs in another body system such as ocular and cardiovascular in one individual.

Revised Ghent Nosology

According to the US National Marfan Foundation, in 2010 the Ghent Nosology was revised, and new diagnostic criteria superseded the previous agreement made in 1996.

The seven new criteria can lead to a diagnosis.

In the absence of a family history of MFS:

1. Aortic root Z-score >/=2 AND ectopia lentis
2. Aortic root Z-score >/=2 AND an FBN1 mutation
3. Aortic root Z-score >/=2 AND a systemic score >7 points
4. Ectopia lentis AND an FBN1 mutation with known aortic pathology

In the presence of a family history of MFS (as defined above):

1. Ectopia lentis
2. Systemic score >/=7
3. Aortic root Z-score >/=2

Points for systemic score

Wrist AND thumb sign = 3 (wrist OR thumb sign = 1)

Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)

Hindfoot deformity = 2 (plain pes planus = 1)

Dural ectasia = 2

Protrusio acetabula = 2

Reduced upper segment/lower segment ratio AND increased arm/height AND no severe scoliosis = 1

Scoliosis or thoracolumbar kyphosis = 1

Reduced elbow extension = 1

Facial features (3/5) = 1 (dolichocephaply, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)

Skin striae = 1

Myopia >3 diopters = 1

Mitral valve prolapse (1D 4) = 1

Differential diagnosis

Many disorders have the potential to produce the same type of body habitus (i.e. shape) as Marfan syndrome. Distinguishing among these "marfanoid" disorders can be facilitated by genetic testing, and by evaluating signs and symptoms other than body habitus. Among the disorders capable of producing a marfanoid body habitus are:

- Congenital contractural arachnodactyly or Beals syndrome
- Ehlers–Danlos syndrome
- Homocystinuria
- Loeys–Dietz syndrome
- MASS phenotype
- Shprintzen–Goldberg syndrome
- Stickler syndrome
- Multiple endocrine neoplasia, type 2B

Management

There is no cure for Marfan's syndrome, but life expectancy has increased significantly over the last few decades, and clinical trials are underway for a promising new treatment. At present (2011), the syndrome is treated by simply addressing each issue as it arises and, in particular, preventive medication even for young children to slow progression of aortic dilation if such exists.

Regular checkups by a cardiologist are needed to monitor the health of the heart valves and the aorta. The goal of treatment is to slow the progression of aortic dilation and damage to heart valves by eliminating arrythmias, minimizing the heart rate, and minimizing blood pressure. Beta blockers have been used to control arrythmias and slow the heart rate. Other medications might be needed to further minimize blood pressure without slowing the heart rate, such as ACE inhibitors and angiotensin II receptor antagonists. If the dilation of the aorta progresses to a significant diameter aneurysm, causes a dissection or a rupture, or leads to failure of the aortic or other valve, then surgery (possibly a composite aortic valve graft or valve-sparing aortic root replacement) becomes necessary. Although aortic graft surgery (or any vascular surgery) is a serious undertaking it is generally successful if undertaken on an elective basis. Surgery in the setting of acute aortic dissection or rupture is considerably more problematic. Elective aortic valve/graft surgery is usually considered when aortic root diameter reaches 50 millimeters (2.0 inches), but each case needs to be specifically evaluated by a qualified cardiologist. New valve-sparing surgical techniques are becoming more common.

The skeletal and ocular manifestations of Marfan's syndrome can also be serious, although not life-threatening. These symptoms are usually treated in the typical manner for the appropriate condition, such as with various kinds of pain medication or muscle relaxants. It is also common for patients to receive treatment from a physiotherapist, using TENS therapy, ultrasound and skeletal adjustment. This can also affect height, arm length, and life span. A physiotherapist can also help improve function and prevent injuries in individuals with Marfan's. The Nuss procedure is now being offered to people with Marfan's syndrome to correct 'sunken chest' or (pectus excavatum). Because Marfan's syndrome may cause asymptomatic spinal abnormalities, any spinal surgery contemplated on a Marfan patient should only follow detailed imaging and careful surgical planning, regardless of the indication for surgery.

Treatment of a spontaneous pneumothorax is dependent on the volume of air in the pleural space and the natural progression of the individual's condition. A small pneumothorax might resolve without active treatment in one

to two weeks. Recurrent pneumothoraces might require chest surgery. Moderately sized pneumothoraces might need chest drain management for several days in a hospital. Large pneumothoraces are likely to be medical emergencies requiring emergency decompression.

Research in laboratory mice has suggested the angiotensin II receptor antagonist losartan, which appears to block TGF-beta activity, can slow or halt the formation of aortic aneurysms in Marfan syndrome. A large clinical trial sponsored by the National Institutes of Health comparing the effects of losartan and atenolol on the aortas of Marfan patients was scheduled to begin in early 2007, coordinated by Johns Hopkins.

References

1. Kainulainen K, Karttunen L, Puhakka L, Sakai L, Peltonen L. Mutations in the fibrillin gene responsible for dominant ectopia lentis and neonatal Marfan syndrome. *Nat. Genet.* 1994; 6 (1): 64–9. doi:10.1038/ng0194-64. PMID 8136837.
2. Dietz HC, Loeys B, Carta L, Ramirez F. Recent progress towards a molecular understanding of Marfan syndrome. *Am J Med Genet C Semin Med Genet.* 2005; 139C(1): 4–9. doi:10.1002/ajmg.c.30068. PMID 16273535.
3. Pyeritz RE. Inherited diseases of connective tissue. In: Goldman L, Ausiello D. *Cecil Medicine*. 23rd ed. Philadelphia, Pa: Saunders Elsevier; 2007: chap 281.
4. Robinson LK, Fitzpatrick E. Marfan syndrome. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BF. *Nelson Textbook of Pediatrics*. 18th ed. Philadelphia, Pa: Saunders Elsevier; 2007:chap 700.
5. Robbins and Cotran Pathological Basis of Disease, Kumar et al; 8th Edition. Saunders Elsevier Publishing, 2010.
6. Brown P (July 27, 1991). "Marfan syndrome linked to gene". *New Scientist*. Retrieved on August 11, 2008.
7. Chen H (June 4, 2007). "Marfan Syndrome". eMedicine. Retrieved June 25, 2007.
8. McKusick V. The defect in Marfan syndrome. *Nature.* 1991; 352(6333): 279–81. Bibcode 1991 Natur.352..279M. doi:10.1038/352279a0. PMID 1852198.
9. Entrez Gene (2007). "TGFBR2 transforming growth factor, beta receptor II" (Entrez gene entry). NCBI. Retrieved January 11, 2007.
10. "Related Disorders: Loeys-Dietz". National Marfan Foundation. Archived from the original on September 25, 2006. Retrieved January 11, 2007.
11. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am. J. Med. Genet.* 1996; 62 (4):417–26. doi:10.1002/(SICI)1096-8628 (19960424)62:4<417::AID-AJMG15>3.0.CO;2-R. PMID 8723076.
12. "Marfan Syndrome — Signs and Symptoms". www.ucsfhealth.org. Retrieved 2009-08-28.
13. "What is Marfan Syndrome?". The Marfan Trust. Retrieved 2009-08-28.[*dead link*]
14. "About Marfan Syndrome: Features". National Marfan Foundation. Retrieved 2009-08-28.
15. "2010 Revised Ghent Nosology". National Marfan Foundation. Retrieved 2011-01-31.
16. Habashi JP, Judge DP, Holm TM, *et al.* Losartan, an AT1 antagonist, prevents aortic aneurysm in a mouse model of Marfan syndrome. *Science.* 2006; 312 (5770): 117–21. Bibcode 2006 Sci...312..117H. doi:10.1126/science.1124287. PMC 1482474. PMID 16601194.
17. "Atenolol vs. Losartan in Individuals with Marfan Syndrome Clinial Trial". National Marfan Foundation. Archived from the original on September 25, 2006. Retrieved January 12, 2007.
18. "Elective Aortic Root Surgery in Marfan Syndrome Appears Safe and Durable: Presented at STS" (Press release). Doctor's Guide. January 31, 2008. Retrieved January 13, 2009.