

Case Reports

Marfan Syndrome in Two Sibs: A Case Report

KONA CHOWDHURY¹, MESBAH UDDIN AHMED², MOHAMMED JAMAL UDDIN³, SUDIPTA ROY⁴

Abstract

Marfan syndrome (MFS) is a rare inherited disorder of connective tissue characterized by various phenotypical and genetic manifestations. It involves mutation in FBN1 gene which encodes for microfibrillin glycoprotein fibrillin-1. Predominant involvement occurs in eyes, skeleton and cardiovascular system. Cardiovascular abnormalities such as aortic root dilatation and mitral valve prolapse are the two main life-threatening complications associated with MFS. The diagnosis is based upon clinical findings, some of which are age dependent. If not properly treated, premature death may be caused by the severe cardiovascular and pulmonary complications associated with Marfan syndrome. Therefore, it is important to identify this potentially life-threatening condition in general practice. We are presenting two cases of Marfan syndrome from same family due to its rarity.

Key Words: Marfan syndrome(MFS)

Introduction

Marfan Syndrome, a disorder caused by an inheritable genetic defect of connective tissue was named after Antonio-Bernard Marfan, a French professor of pediatrics who presented a case of this rare disease in a 5-year-old female with disproportionately long limbs.¹ This disorder is caused by mutations in the gene encoding the extracellular matrix protein fibrillin-1.²⁻⁵ It is primarily associated with skeletal, cardiovascular and ocular pathology.² The disorder presents with varying degrees of expressivity and penetrance.^{2,5}

The diagnosis is commonly considered in a young person with a tall, thin body habitus, long limbs, arachnodactyly, pectus deformities, and sometimes scoliosis. Other clinical findings such as a high arched palate with dental crowding, skin striae, recurrent hernia or recurrent pneumothorax may increase suspicion. Family history may be helpful, but around 27% of cases arise from new mutation.⁶ Patients often remain oblivious of underlying systemic defects and may suddenly be faced by serious life-threatening sequelae

in adulthood, the most fatal ones being cardiovascular in nature.⁷ Progressive aortic dilatation, usually maximal at the sinus of Valsalva, associated with aortic valve incompetence leads to aortic dissection or rupture and is the principal cause of mortality, but mitral valve prolapsed with incompetence may be significant, and lens dislocation, myopia, and arthritis associated with chronic joint laxity can cause substantial morbidity.⁶

No single sign is pathognomonic for MFS. Given the complexity of the clinical manifestation and the relevant differential diagnoses, the diagnosis is based on a defined set of clinical criteria drawn up by an international panel of experts; revised Ghent nosology for the MFS.² We are presenting two cases of MFS from the same family because of its rarity and to highlight the need of early diagnosis to avert the numerous complications that follow it.

Case – 1

A 12 year old male child presented in our department with H/O dyspnea while playing for ten days. The boy was tall (HAZ on 95th centile), thin and slender with disproportionate long arm and legs as compared to trunk. His arm span was more than height by about 5 cm. Arm span to height ratio was 1.04 and upper segment to lower segment ratio was 0.86. He had elongated fingers with thickening of phalange joints (Figure-1). Walker Murdoch wrist sign (Figure -2) and Steinberg thumb sign (Figure-3) were positive. He also had elongated face, malar hypoplasia, high arched palate and pes planus (Figure-4). Echocardiography revealed mild mitral valve prolapse of AML.

1. Associate Professor, Paediatrics, Gonoshasthaya Samaj Vittik Medical College & Hospital
2. Professor, Department of Paediatrics, Gonoshasthaya Samaj Vittik Medical College & Hospital
3. Assistant Professor, Paediatrics, Jahurul Islam Medical College & Hospital
4. Assistant Professor, Paediatrics, Ad-din Women's Medical College & Hospital

Correspondence : Dr. Kona Chowdhury, Associate Professor & Head, Department of Paediatrics, Gonoshasthaya Samaj Vittik Medical College & Hospital, Dhaka. Cell No. 01830010566, email: konachy56@yahoo.com

Received: 8/02/2021

Accepted: 21/07/2021



Fig.-1



Fig.-2

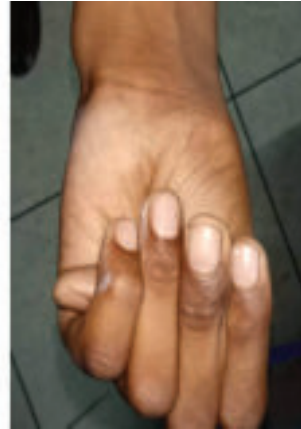


Fig.-3



Fig.-4



Fig.-5

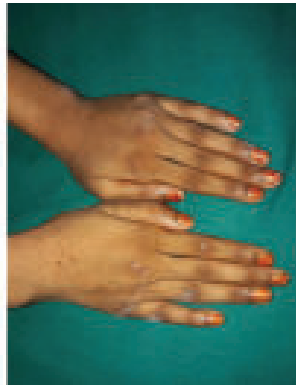


Fig.-6



Fig.-7



Fig.-8

Case – 2

Another 7 year old girl, younger sister of the first case, also suffered from exertional breathlessness for last four months and was being treated with tablet enalapril and propranolol advised by a cardiologist. She was also thin and slender (Figure-5) with elongated face, downward palpebral fissure, malar hypoplasia, arm span to height ratio 1.01, upper segment to lower segment ratio 0.88, elongated fingers with thickening of phalangeal joints (Figure-6), positive wrist (Figure-7) and thumb sign (Fig-8). Her echocardiography also revealed mild Mitral valve prolapse with moderate mitral regurgitation.

Father of these two children died suddenly at 32 years of age in 2015 due to cardiac cause and according to mother he also had similar features.

Discussion

Marfan syndrome (MFS) is an inherited genetic disorder, primarily affecting the connective tissue. The connective tissue is made up of various proteins, including fibrillin-1 (FBN1). FBN1 serves as the main

structural component of microfibrils in the extracellular matrix (ECM). These microfibrils incorporate elastin into elastic fibers, thus forming the structural framework. MFS is caused by mutations in the FBN1 gene, which causes misfolding/alteration of FBN1 protein. MFS has a low incidence rate, and it occurs with similar frequency across all countries, races, and genders. It is a long-lasting and life-threatening disease affecting multiple vital organs simultaneously, with cardinal manifestations in the skeletal, cardiovascular and ocular system.^{2,4} Most patients who have Marfan syndrome are usually diagnosed incidentally when they present for a routine physical examination. Typically, patients with Marfan syndrome present with tall stature, ectopia lentis, aortic root dilatation, and a positive family history. Less frequently, the diagnosis is made when a patient presents with complications of the syndrome, such as aortic dissection, or with involvement of the pulmonary, skin/integument, or nervous systems.⁶

Skeletal manifestations are the cardinal signs of Marfan syndrome and usually gain the attention of a

physician. The most common features include tall stature with the lower segment of the body greater than the upper segment and long, slender limbs, or dolichostenomelia; thin body habitus with increased arm span-to-height ratio; long, slender fingers, or arachnodactyly; deformities of the chest, such as pectus carinatum or pectus excavatum, scoliosis and highly arched palate with crowded teeth and dental malocclusion. Other less common manifestations include hypermobility of joints, flat foot (pes planus), reduced extension of elbows ($<170^\circ$), and elongated face (dolichocephalia). Most of the features were seen in the present two cases except hypermobility of joints. Patients should be examined for arachnodactyly; positive wrist or Walker's sign (the distal phalange of the first and fifth fingers of the hand overlap when wrapped around the opposite wrist); and positive thumb or Steinberg sign (the thumb projects beyond the ulnar border while completely opposed within the clenched hand which were positive in both the cases).^{2,8}

Within the heart thickening of atrioventricular (A-V) valve is common and often associated with valvular prolapse. Variable degree of regurgitation may be present. Aortic aneurysm, dissection and rupture, particularly at the level of the sinuses of valsalva (aortic root) remain the most life threatening complications of MFS, prompting life long monitoring by echocardiography. The most important risk factors for aortic dissection are the maximal aortic root size and a positive family history.^{2,3} Both cases had mitral valve prolapse along with regurgitations in second case. Ectopia lentis (subluxation of lens) occurs in approximately 60% to 80% of patients and often associated with myopia, flat cornea and hypoplastic iris.² Ophthalmological examination of both of our patients revealed no abnormality. Striae may occur over the shoulders and buttocks. Pulmonary manifestations include spontaneous pneumothorax and apical blebs. Marked dilatation of the dural sac may be seen frequently in computed tomography or magnetic resonance imaging scans, but the condition is usually asymptomatic.^{2,8}

Owing to the multiorgan nature of the disease, the diagnosis of MFS becomes very challenging.³ the diagnosis is based on a defined set of clinical criteria drawn up by an international panel of experts ; revised Ghent nosology for the MFS.^{2,3,9} MFS was diagnosed in our setup on clinical ground due to financial constrain diagnosis was not confirmed by genetic study. Management mainly focuses on preventing complications and genetic counseling and requires multidisciplinary approach.² Current therapies include activity restrictions, aortic surgery, awareness of possible complications before pregnancy, antibiotic prophylaxis against bacterial endocarditis in selected groups, beta Blockers and angiotensin II receptor blockers.²

References

1. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996; 62: 417-26.
2. Doyle A, Doyle JJ, Dietz H C. Marfan Syndrome In: Behrman R., Kliegman R., Stanton, editors. *Nelson Textbook of Pediatrics*. 20th ed. Elsevier Science; Philadelphia: Saunders, 2016: 3384-89.
3. Pepe G, Giusti B, Sticchi E, Abbate R, Gensini GF, Nistri S. Marfan syndrome: current perspectives. *Appl Clin Genet*. 2016;9:55-65.
4. Matkar PN, Chen HH, Leong-Poi H, Singh KK. Overview of Marfan Syndrome: Knowns and Unknowns. *Journal of Controversies in Biomedical Research* 2015; 1:51-66.
5. Von Kodolitsch Y, Robinson PN. Marfan syndrome: an update of genetics, medical and surgical management. *Heart* 2007;93:755-60.
6. Dean JC. Marfan syndrome: Clinical diagnosis and management. *Eur J Hum Genet* 2007;15:724-33.
7. Allwork SP, Miall-Allen VM, Wyse RK, et al. Cardiovascular disease in Marfan patients in infancy and childhood. In: Hetzer R, Gehle P, Ennker J, editors. *Cardiovascular aspects of Marfan syndrome*. Darmstadt, Germany: Steinkopff Verlag, 1995:17-23.
8. Gray JR, Bridges AB, West RR, McLeish L, Stuart AG, Dean JC, et al. Life expectancy in British Marfan syndrome populations. *Clin Genet* 1998;54:124-8.
9. G Faivre, Gwenaëlle Collod-Bérout, A Ades, A Arbustini, C Child, et al. The new Ghent criteria for Marfan syndrome: what do they change?. *Clin Genet*, Wiley, 2012; 81: 433-42.