Marfan Syndrome with Atypical Presentation: A Case Report

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Abstract:

Marfan syndrome is an inherited connective tissue disorder that is transmitted as an autosomal dominant trait. These cases can be diagnosed by molecular cytogenetic techniques. A modified Ghent criteria using systemic scoring system can also identify these cases in absence of molecular cytogenetic techniques.We report a case of a 6 year 5 month old boy who presented with the complaints of excessive sweating since infancy and protrusion of both eye balls which was non progressive since early childhood. On examination, some skeletal features of Marfan syndrome was found and echocardiogram showed huge dilatation of root of aorta which helped in diagnosis by scoring system.

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Introduction:

Marfan syndrome is an inherited connective tissuedisorder that is transmitted as an autosomal dominant trait and is named after the French pediatrician AntoineBernard Marfan, who first summarized the symptoms in 1892.[1] He reported the association between slender digits andspecific skeletal abnormalities in a 5 year old girl called Gabrielle who had disproportionately long limbs that Marfan termed "arachnid-like" or "spider-legs".[2]

Being a connective tissue disorder, Marfan syndrome mostly affects skeleton, lungs, eyes, heart, and the aorta.[3] Myxomatous degeneration of aortic valve, lens dislocation, pectusexcavatum, arachnodactyly, dilatation of aorta are the classical features of Marfansyndrome.[4,5] Affected individuals often are tall and slender, have arachnodactyly, scoliosis, and either a pectusexcavatum, pectuscarinatum, or ectopialentis in eyes.[6] Here we present a case recently seen in Bangladesh Institute of Research and Rehabilitation in Diabetic, Endocrine and Metabolic disorders (BIRDEM) hospital, in order to create further awareness and highlight the importance of proper diagnosis and management of this rare disorder as may be applicable in our setting.

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Case Report:

A 6 year 5 month old boy presented with the complaints of excessive sweating since infancy and protrusion of both eyeballs which was non progressive since early childhood. There was no history of headache, vomiting, visual disturbance, weight loss, palpitation, tremor or intolerance to heat. He had history of recurrent cough and acute respiratory tract infection since 1 year of age. Developmental history revealed motor and speech delay. On examination, he was thin and slender having narrow facies with, protruded eyeballs, broad based nasal bridge and high arched palate. His vital parameters were normal. He was tall for his age with significant longer arm span. He was 128.2 cm tall and his arm span length was 134.5 cm.His upper segment to lower segment ratio was 0.9:1 (Normal upper segment to lower segment ratio is 1:1 for his age). His arm span to height ratio was 1.05:1 (Normal arm span to height ratio is less than 1 for his age). His weight was19 Kg (Below 25th centile for his age and sex) and Body Mass Index (BMI) was 11.59 Kg/m^2 (Below 5^{th} centile for his age and sex). The fingers and toes of this patient were characteristically long, giving rise to the arachnodactyly or spider- fingers (Fig.-2). He had both pectus excavatum and pectus carinatum with kyphosis and scoliosis of thoracolumbar vertebrae (Fig.-1). The distal phalanx of his thumb extended beyond the ulner border of his hand when folded across the palm which is known as Steinberg or thumb sign (Fig.-3). There was full overlap of the distal phalanges of the thumb and fifth finger when wrapped around his

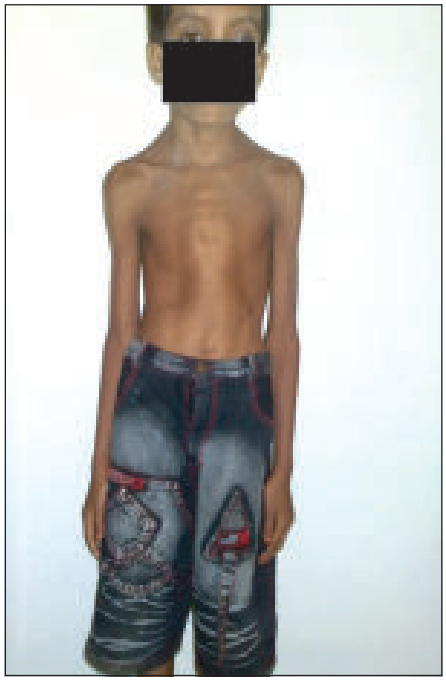

Fig.-1: *Patient having slender body, pectuscarinatum, pectusexcavatum and mild scoliosis*

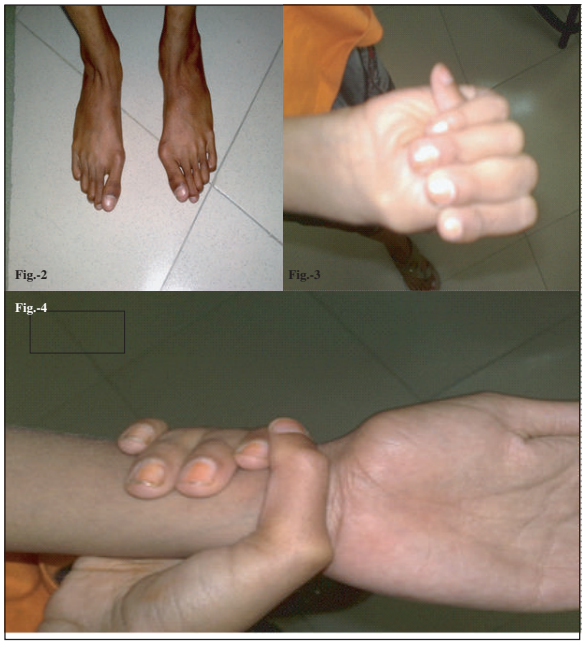

Fig.-2: *Arachnodactyly,* **Fig.-3:** *Thumb sign,* **Fig.-4:** *Wrist sign*

contra lateral wrist, which is known as Walker-Murdoch or wrist sign (Fig.-4). There was no hypermobility of joints. Thyroid gland was not enlarged. Heart sounds were normal and there was no murmur.Neurological examination was normal. Other systemic examinations revealed normal findings. There was no history of consanguinity and no other family members had similar features. Ophthalmic examination was done which was normal and there was no ectopialentis. Thyroid function test and X-ray chest were normal. X-ray skull including the bony orbit revealed normal findings. X-ray thoracolumbar spine showed mild scoliosis andelectrocardiogram was normal.Echocardiogram showed huge dilatation of root of the aorta of 37mm (Fig.-5).The child was diagnosed as a case of Marfan syndrome. Cardiac consultation was taken and propanolol and enalapril were given to reduce the cardiac load. A follow up echocardiogram was advised after 6 months. Counseling of the parents was done regarding the nature of the disease. Genetic counseling was done. We advised for regular follow up with emphasis on yearly evaluation for cardiovascular, ophthalmological and orthopedic problem. Patient was advised not to perform strenous physical exertion such as competitive athletics and isometric activities like weight lifting which may increase the risk of aortic and ocular complications.

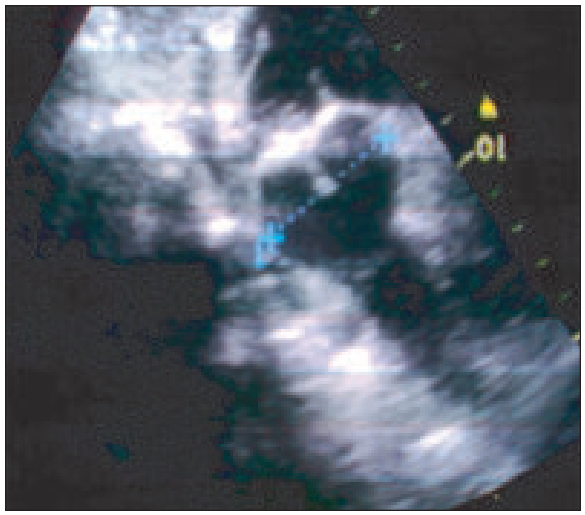

Fig.-5: *Dilatation of the root of aorta*

Discussion:

Marfan syndrome (MFS) is a dominant disorder, mainly caused by mutations in the fibrillin-1 gene (FBN1) located on chromosome 15q21.1. Approximately 25% MFS patients are sporadic cases due to new mutation.[7,8] Worldwide, the incidence of Marfan syndrome is approximately 2-3/10000.[9] Diagnosis is usually missed

because patients may be taken as extremes of normal. In 1986, a defined set of clinical criteria (Berlin nosology)[10] for the diagnosis of MFS was introduced with the aim of facilitating accurate communication about the condition among healthcare providers, researchers and patients. Following the identification of the FBN1 gene (encoding fibrillin-1) as the causal gene, a new diagnostic criterion referred to as the Ghent nosology[11] was introduced to minimize false-positive diagnoses made with the Berlin criteria. The Ghent nosology employed a set of 'major' and 'minor' manifestations in numerous tissues, including the skeletal, ocular, cardiovascular, and pulmonary systems, the dura, skin and integument. A revision of the criteria has recently been published (2010 Ghent nosology)[12] with added weight given to two cardinal features of MFS: aortic root aneurysm/dissection and ectopialentis. In the absence of findings that are not expected in MFS, the combination of ectopialentis and aortic root enlargement/ dissection should be sufficient to make the diagnosis. All other cardiovascular and ocular manifestations of MFS and findings in other organ systems, such as the skeleton, dura, skin and lungs, contribute to a 'systemic score' that guides diagnosis when aortic disease is present but ectopialentis is absentand the FBN1 status is either unknown or negative. In that case diagnosis of MFS is confirmed by the presence of aortic root dilatation (z- score e"2) and sufficient systemic findings (e"7points).[12,13]Although our patient initially presented with excessive sweating and prominent eyeballs which was non progressive, after thorough clinical examination both pectusexcavatum and pectuscarinatum (score 3) with kyphosis and scoliosis of thoracolumbar vertebrae (score 1) were found.Both Steinberg or thumb sign and Walker-Murdoch or wrist sign (score 3) were present.He had reduced upper segment to lower segment ratio and increased arm to height ratio and no severe scoliosis (score1). Our patient had huge dilatation of root of the aorta of 37mm on echocardiogram and a systemic finding of 8 points. Thus our patient met the diagnostic criteria using the 2010 Ghent nosology.

Our patient presented with unusual presentation having prominent eyeballs and excessive sweating which was non progressive. For proptosis we had some differential diagnosis in our mind like Hyperthyroidism and Crouzon syndrome. Hyperthyroidism was excluded by doing thyroid function test. Except proptosis our patient did not have any typical characteristics of Crouzon syndrome such as parrot beak nose and maxillary hypoplasia and history of premature closure of sutures (craniosynostosis). Thus Crouzon syndrome was excluded. Homocystinuria and Congenital contracturalarachnodactyly syndrome were considered as differential diagnosis due to presence of some skeletal features as found in our patient. As the boy did not have mental retardation and typical ocular findings, homocystinuria was excluded. Congenital contracturalarachnodactyly syndrome presents with contracturalarachnodactyly only. As our patient did not have any contracture and also had huge dilatation of aorta and typical skeletal abnormalities of Marfan syndrome, congenital contracturalarachnodactyly syndrome was also excluded.

Ganesh R et al[14] reported a case of Marfansyndrome with unusual presentation of cranio stenosis, hypothyroidism and intellectual deficit. They commented that most probably the underlying cause was deletion involving other genes besides FBN1. Hutchison et al[15] suggested that the clinical variability in MFS could be due to variable FBN1 expression of the normal allele which could also be applicable to our patient though genetic study for FBN1 gene was not possible in this case.Our patient showed most of the skeletal features of MFS and aortic root dilatation, but no ectopialentis, which was consistent with features found by Colovati MESet al.[8] Though eye examination was normal in our patient, yet the eye evaluation should be performed every year. Individuals with MFS are at increased risk for glaucoma, cataract formation and retinal detachment even in the absence of ectopialentis. Progression of skeletal abnormalities can be dramatic during periods of rapid growth, such as puberty. Follow up by an Orthopedist is indicated in these cases. They require frequent assessment of the status of the aortic root, with a maximal interval between echocardiogram of one year. In the presence of ascending aorta dilatation, prophylactic surgery is recommended when the diameter of the ascending aorta at the aortic sinuses reaches 4.5 cm, or in some cases even less (when there is a family history of aortic dissection, in the presence of rapid aortic dilatation or severe aortic valve regurgitation, or when a valve-sparing operation is possible).[9,16]In our patient, the presence of aortic root dilatation (37 mm) was not a clear indication for surgery. The prognosis

for patients with Marfan syndrome is highly variable. Although generally the life span has been reported to be approximately 32 years of age; in recent publication, the average life expectancy for people with MFS approaches normal, particularly in those who underwent aortic root surgery after 1980.[13,16] Cardiovascular complications are the predominant cause of death in these patients, aortic dissection (38%), fusiform ascending aortic aneurysm (35%) and mitral regurgitation (22%) being the commonest post-mortem findings.[17]

We emphasize on the importance of systemic scoring system to diagnose Marfansyndrome even when molecular cytogenetic study is not possible. Our patient had unusual presentations and could have been missed; but he was diagnosed as a case of Marfansyndrome using systemic scoring system of modified Ghent criteria 2010 by thorough clinical examination.

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References:

1. Gott VL. Antoine Marfan and his syndrome: one hundred years later. Md Med J. 1998 ;47(5): 247-52.
2. Ng DK, Chau KW, Black C, Thomas TM, Mak KL, Boxer M. Neonatal Marfan syndrome: a case report. J Paediatr Child Health1999; 35(3): 321-23.
3. Gonzales EA. Marfan syndrome. J Am Acad Nurse Pract: 2009;21: 663-70. 4. Shirley ED, Sponseller PD.Marfan syndrome. J Am Acad Orthop Surg 2009; 17(9): 572-81.
5. Johnson WMS, Johnson P. Marfan syndrome - a case report. Anatomica Karnataka 2012; 6: 35-39.
6. Diop IB, BaSA, Sarr M et al. "Cardiovascular manifestations of Marfan's syndrome apropos of 6 cases," Dakar Medical 1994; 39(2): 231–36.
7. Hilhorst-Hofstee Y, Hamel BC, Verheij JB, Rijlaarsdam ME, Mancini GM, CobbenJM et al. The clinical spectrum of complete FBN1 allele deletions. European Journal of human genetics 2011; 19 (3): 247-52.
8. Colovati MES, Silva LRJD, Takeno SS, Mancini TI, Dutra ARN, Guilherme RS et al. Marfan syndrome with a complex chromosomal rearrangement including deletion of the FBN1 gene- case report. Molecular cytogenetics 2012; 5: 1-5.
9. Ammash NM, Sundt TM, Connolly HM. Marfan syndrome-diagnosis and management. Curr Probl Cardiol. 2008; 33: 7-39.
10. Beighton P, De Paepe A, Danks D, et al. International nosology of heritable disorders of connective tissue, Berlin, 1986. Am J Med Genet 1988;29:581-94.
11. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 1996;62:417-26.
12. Loeys BL, Dietz HC, Braverman AC, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet 2010;47:476-85.
13. Doyle J, Dietz H. Marfan Syndrome. In: Kliegman RM, St. Geme JW, Schor NF, Behrman RE, Stanton BF, editors. Nelson Textbook of Pediatrics. 19th ed. Philadelphia (PA): Elsevier; 2012: 2440-46.
14. Ganesh R, Vijayakumar R, and Selvakumar H.Marfan Syndrome: A Case Report.Case Reports in Dentistry 2012; 3: 1-4.
15. Hutchison S, Furger A, Halliday D, Judge DP, Jefferson A, Dietz HC et al. Allelic variation in normal human FBN1 expression in a family with Marfan syndrome: a potential modifier of phenotype? Human molecular genetics 2003; 12(18): 2269-76.
16. Vahanian A, Baumgartner H, Bax J. Guidelines on the management of valvular heart disease: The Task Force on the Management ofValvularHeart Disease of the European Society of Cardiology.Eur Heart J 2007;28: 230-68.
17. Roberts, W.C. &Honig, H.S. The spectrum of cardiovascular disease in the Marfan syndrome: A clinic morphologic study of 18 necropsy patients and comparison to 151 previously reported necropsy patients. Am Heart J 1982, 104: 115-35.