Severe aortic root dilatation in infantile Marfan syndrome

Renita A. Thomas, BS^a , Chikamuche T. Anyanwu, BS^a , Maria Blazo, MD^{a,b}, and Saradha Subramanian, MD^{a,c}

^aCollege of Medicine, Texas A&M University Health Science Center, Bryan, Texas; ^bDepartment of Genetics, Baylor Scott & White Medical Center–Temple, Temple, Texas; ^cDepartment of Pediatric Cardiology, Baylor Scott & White McLane Children's Medical Center, Temple, Texas

ABSTRACT

Cardiovascular manifestations of Marfan syndrome are associated with increased mortality, especially in the pediatric population. Early recognition is critical to long-term management. We present two cases of genetically defined “classical” Marfan syndrome presenting with severe infantile aortic root dilatation among siblings and discuss options for therapy.

KEYWORDS Aortic valve dilatation; classical Marfan syndrome; FBN1; fibrillin; neonatal Marfan syndrome

The “classic” Marfan syndrome (MFS) is an inherited autosomal dominant systemic connective tissue disorder affecting 2 to 3 per 10,000 individuals.^{1–4}

Mutations in the *FBN1* gene, which is located on chromosome 15 and encodes the extracellular matrix glycoprotein fibrillin-1, are the genetic basis for its pathology. Cardinal manifestations of MFS involve the musculoskeletal, pulmonary, ocular, integumentary, and cardiovascular systems. Variability in severity and phenotypic presentation makes MFS a diagnostic challenge. Despite advancements in diagnostic capabilities and greater usage of genetic testing, there is a high degree of variability in the phenotypic manifestation of MFS in individuals (*Table 1*).⁵ We report two siblings with infantile MFS with varying presentation and severe changes in cardiac morphology.

CASE DESCRIPTIONS

The first patient was a 14-month-old male born at 40 weeks via uncomplicated spontaneous vaginal delivery. He presented with an abnormally shaped head, pectus carinatum, scoliotic curvature to his spine, abnormally long digits, and flat feet. Genetic testing revealed the same mutation of *FBN1* as his mother, who had a known medical history of MFS. Cardiac exam was unremarkable. The echocardiogram showed significant findings. The second patient was a 7-month-old female born at 37 weeks via uncomplicated spontaneous vaginal delivery. Genetic testing revealed the same mutation as her brother and mother. Cardiac exam was unremarkable. Echocardiogram (*Figure 1*) revealed a small secundum atrial septal defect with

left-to-right shunt. The aortic root measurements and clinical findings for the patients are summarized in *Table 2*. Both infants had a severely dilated aortic root with effacement of the sinotubular junction. The first patient had more prominent dilation of the aortic valve. Both were placed on propranolol and losartan with routine echocardiograms. The infants' pedigree appears in *Figure 2*.

DISCUSSION

The patients presented in this report were siblings with familial MFS. Both presented with the heterozygous intronic variant c.IVS46 + 5 G > A (c.5788 + 5 G > A) mutation on intron 46 of *FBN1*, similar to their mother. Analysis of the variant in the Universal Mutation Database for Marfan syndrome (UMD-FBN1) indicated that the mutation is a temperature-sensitive small rearrangement affecting Ca²⁺ binding of the fibrillin-1 protein. This mutation causes a skipping of exon 46, in frame at the mRNA level, that produces a splicing variant of approximately –13.8% from the wild type sequence.⁶ Twenty-nine events of the same mutation as our patients have been logged in the UMD-FBN1 database. Though limited, the phenotypic manifestations of the individuals listed in the database revealed variations in clinical presentation despite having the same genetic mutation, further demonstrating that genotype variation does not correlate consistently with phenotypic manifestation of MFS. This may suggest that genotypic variation in MFS does not correlate with the phenotypic manifestation of the disease.

Corresponding author: Renita A. Thomas, BS, College of Medicine, Texas A&M University Health Science Center, 346 Redstone Dr., Sunnyvale, TX 75182 (e-mail: renita.thomas@tamu.edu)

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Table 1. The 2010 revised Ghent nosology for Marfan syndrome

Family history	Rules
Absent	<ol style="list-style-type: none"> 1. Aortic root dilatation (Z score ≥ 2) and ectopia lentis^a 2. Aortic root dilatation (Z score ≥ 2) and <i>FBN1</i> 3. Aortic root dilatation (Z score ≥ 2) and systemic score ≥ 7 points^a 4. Ectopia lentis and <i>FBN1</i> mutation with known aortic root dilatation
Present	<ol style="list-style-type: none"> 1. Ectopia lentis and family history of Marfan syndrome (as defined above) 2. Systemic score ≥ 7 points and family history of Marfan syndrome (as defined above)^{a,b} 3. Aortic root dilatation (Z score ≥ 2 above 20 years old, ≥ 3 below 20 years old) + family history of Marfan syndrome (as defined above)^a

^aWithout discriminating features of Shprintzen Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers Danlos syndrome and after *TGFBR1/2*, collagen biochemistry, and *COL3A1* testing if indicated; other conditions/genes will emerge with time.

^bTo obtain the systemic score, add points in parentheses if present: Wrist and thumb sign (3), wrist or thumb sign (1), pectus carinatum deformity (2), pectus excavatum or chest asymmetry (1), hindfoot deformity (2), plain flat foot (pes planus) (1), pneumothorax (2), dural ectasia (2), protrusio acetabulae (2), reduced upper segment/lower segment and increased arm span/height ratios (1), scoliosis or thoracolumbar kyphosis (1), reduced elbow extension (1), three of five facial features (1), skin striae (1), myopia (1), mitral valve prolapse (1).

Table 2. The patients' clinical and echocardiogram findings

	Case 1 ^a	Case 1 ^a	Case 2
Age (months)	19	20	7
Sex	Male	Male	Female
Mutation	<i>FBN1</i> , c.5788 + 5G > A	<i>FBN1</i> , c.5788 + 5G > A	<i>FBN1</i> , c.5788 + 5G > A
LVEF	62%	60%	55%
AV dilation	Not classified	Moderate to severe	Mild
AR dilation	Severe	Severe	Severe
AR diameter length (cm, Z score)	2.40 (+5.4)	2.6 (+6.6)	2.1 (+6.6)
Aorta at ST diameter (cm, Z score)	Unmeasured	1.7 (+3.4)	1.4 (+3.1)
Aortic annulus diameter (cm, Z score)	1.4 (+2.4)	1.7 (+3.4)	1.2 (+2.7)

AV indicates aortic valve; AR, aortic root; *FBN1*, fibrillin-1; LVEF, left ventricular ejection fraction; ST, sinotubular.

^aCase 1 had an initial echocardiogram and a subsequent echocardiogram 1 month later. Both echocardiograms were done prior to any pharmacologic interventions.

Figure 1. (a) The aortic root diameter measured 2.6 cm with a Z score of +6.6. (b) The aortic root diameter measured 2.1 cm with a Z score of +6.6. Ar indicates aortic root; Ao, aorta.

Cardiovascular abnormalities are present in virtually all adults with MFS, with >90% of premature deaths in MFS due to cardiovascular complications.³ MFS-related cardiac abnormalities include aortic root dilatation, pulmonary artery dilatation, valvular stenosis, prolapse, and regurgitation, which may lead to dissections, arrhythmias, or endocarditis.^{2,3} Affecting 60% to 80% of patients with MFS, aortic root dilatation is by far the most common complication in both adult and pediatric populations.^{2,3,7} The incidence of aortic root dilatation increases with age, affecting 35% of patients prior to 5 years of age and increasing to over 70% of patients prior to age 20 years.⁸ This discrimination in age presentation contributes to the challenge in diagnosing and managing MFS in early childhood, because the features are mild and easily missed on clinical examination.³ Though most children with MFS have aortic root dilatation, cases such as ours of infantile aortic root dilatation are exceedingly rare. Aortic root dilatation in children is a common feature seen in “neonatal” MFS (nMFS), a severe

form of MFS often associated with deletions in exons 24 to 32 of *FBN1*. This condition differs from classical MFS in that there is an earlier age of onset, rapid progression, increased severity of cardiac and pulmonary manifestations, and increased mortality.^{3,8}

The siblings in this report presented with the severe features of nMFS. However, the mutation in their *FBN1* intron differs from the traditionally seen exonic mutation in nMFS. A PubMed search of case reports on MFS and aortic root dilatation in infants 0 to 23 months of age yielded few results. Review of the literature revealed that most cases of aortic root dilatation are associated with nMFS.^{9–11} Other reports failed to mention the genetic mutation observed or the presence of aortic root dilation.¹² Thus, to our knowledge, this report describes the first case of infantile aortic root dilatation in classical MFS.

Management of cardiovascular manifestations in MFS is centered on surveillance and prevention. Annual echocardiograms are recommended in patients with relatively small aortas or with slower rates of aortic dilation.² Surveillance intervals decrease with increased aortic diameter (>4.5 cm in adults), greater rates of aortic dilation (>0.5 cm/year), or severe aortic regurgitation.² Pharmacological management of cardiovascular abnormalities in MFS has been controversial. Studies indicated some effectiveness in the use of beta-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors.^{2,3,7} Limitations linked to the studies involved low sample sizes, nonrandomization, and atypical dosing of study groups.

Figure 2. The pedigree of both infants. The infant boy and infant girl are numbers 4 and 2, respectively. Additionally, their relatives' associated ages, heights, medical histories, and ages of diagnosis are provided. CAD indicates coronary artery disease; CHD, congenital heart disease; d, died at age; Dx'd, diagnosed; MI, myocardial infarction; MVA, motor vehicle accident; Unk, unknown.

Groundbreaking results by Habashi et al in 2006 led to the use of angiotensin receptor blockers (ARBs) in preventing aortic root dilatation. Their study revealed that losartan played a role in halting abnormal aortic root dilation in mouse models.¹³ The theory was that antagonism of transforming growth factor beta (TGF-beta), which is excessively produced in MFS, may attenuate many of the manifestations involved in the disease. TGF-beta plays a role in vascular smooth muscle proliferation, aortic root dilation, and aortic aneurysm formation. Angiotensin II receptor type 1 has been shown to activate TGF-beta; thus, ARBs serve as therapeutic agents in combating aortic root dilation.⁴

This theory was tested clinically in the COMPARE trial. The study by Groenink et al showed a significant reduction in aortic root dilatation rates in the aortic root and aortic arch in adults following losartan therapy.¹⁴ Systematic reviews on adults with MFS indicated better protection against aortic root dilation with angiotensin-converting enzyme inhibitors or ARBs than beta-blockers.^{2,7} Studies on pharmacological management of pediatric patients with MFS have, however, yielded inconclusive results. Despite trials indicating that ARBs have efficacy similar to that of beta-blockers, some experts continue to recommend losartan as first-line treatment to reduce the rate of aortic root dilation in pediatric patients.^{2,10} Combination therapy may offer better protection against aortic dilation.²

Surgical intervention for aortic root dilation should be considered with increasing rates of aortic dilation up to 0.5 to 1 cm per year or with progressive severe aortic regurgitation. Many pediatric centers adopt adult guidelines for surgical management of aortic root dilation.² Reports have shown improved survival in patients with MFS who undergo corrective cardiac surgery.^{3,4,15} Due to the small number of reported cases, we are skeptical of the effectiveness of cardiac surgical intervention in the pediatric population with MFS.

In conclusion, we present a novel presentation of a well-known disease with fatal complications. Whether our

findings suggest a new variation in "nMFS" or a new manifestation of MFS on its own is still to be determined. Further studies on genetic linkages with certain phenotypic manifestations may provide insights on the development of clinical features seen in MFS.

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ORCID

Renita A. Thomas <http://orcid.org/0000-0001-7267-2138>

Chikamuche T. Anyanwu <http://orcid.org/0000-0002-0081-2290>

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