Early-Onset Marfan Syndrome: A Case Series

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J Pediatr Genet 2019;8:86–90.

Abstract

Keywords

- Marfan syndrome
- mitral valve prolapse
- aortic root dilatation
- *FBN1* gene

Mutations in fibrillin 1 cause Marfan syndrome (MFS), an autosomal dominant disorder of the connective tissue, with multisystem manifestations. In early-onset MFS, the physical characteristics are expressed much earlier than the classical MFS. Those affected by this form generally have their mutations restricted to the gene “hotspot” region of exons 24 to 32. Historically, affected individuals usually die within the first few years of life due to heart failure secondary to severe valvular insufficiency. We report three patients with early-onset MFS, whose clinical evolution has been remarkably positive, when compared with other reported cases in the literature.

Introduction

Marfan syndrome (MFS) is an autosomal dominant disorder of the connective tissue with variable expressivity, with a reported incidence of 1 in 5000, caused by mutations in *FBN1* gene. This gene encodes fibrillin-1 protein, which in turn polymerizes into microfibrils. Fibrillin microfibrils are present in all connective tissues and interact with basement membrane providing rigidity to the extracellular matrix. Microfibrils impart the natural elasticity to the skin, ligaments, and blood vessels. They also provide support to the tissues that surround nerves, muscles, and lenses of the eyes. In MFS, cardiovascular, ocular, and skeletal systems are typically affected the most. In addition, lungs, dura mater, and skin are also often involved.¹ One of the pathogenic mechanisms of MFS is thought to be a paradoxical increase in tumor growth factor beta (TGF- β) caused by an abnormal fibrillin-1 activity, demonstrated by an increased level of TGF- β in the aortic wall of fibrillin-1-deficient mice. TGF- β is thought to play a role in the proliferation of vascular smooth muscle cells and may result in aortic root dilatation. Angiotensin II receptor type 1 activation also increases the production of TGF- β . Selective inhibition of the AT1 receptor offers a therapeutic target to modify the pathogenesis of tissue injury in MFS.

Early-onset MFS is an extremely rare subtype of the disorder where the phenotype may be expressed in the antenatal, neonatal, or infancy period, much earlier than that seen in classical MFS. This early-onset group is sometimes referred to as infantile form of MFS. The exact frequency of this subtype among the patients with MFS phenotype is currently not available in the literature. In those affected by the infantile form of MFS, the mutation in *FBN1* is generally restricted to exons 24 to 32, which has been referred to as the “hotspot.” This led to the hypothesis that this region has a more critical role in the function of fibrillin-1 protein, thereby resulting in earlier and more severe disease manifestations.² Historically, the affected individuals usually die within the first few years of life. Unlike classical MFS, where death is often due to acute aortic dissection and rupture, patients with this early-onset form die from congestive heart failure (CHF) secondary to severe cardiac valvar insufficiency.^{3–5} The rarity of this disease coupled with a high mortality during early childhood makes the prognosis and disease progression difficult to predict.^{6,7} We report three patients with early-onset or infantile MFS, whose clinical evolution has been remarkably positive, when compared with other reported cases in the literature.^{8–10} Two of these patients had their mutation in the reported “hotspot” region.

received

August 8, 2018

accepted after revision

September 17, 2018

published online

November 2, 2018

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Verlag KG, Stuttgart · New York

DOI <https://doi.org/10.1055/s-0038-1675338>.
ISSN 2146-4596.

Case Series

Patient 1

Patient 1 is a 12-year-old female who was born full term as a first child of healthy nonconsanguineous parents. There is no family history of individuals with physical features of MFS. On physical examination at birth, she had dysmorphic features including arachnodactyly, loose facial skin giving a “senile appearance,” deep-set eyes, high-arched palate, retrognathia, and pectus carinatum along with length > 99th percentile. Ophthalmologic examination at birth revealed no lenticular dislocation. Cardiac examination revealed a grade 2/6 apical holosystolic murmur. Initial echocardiogram at birth demonstrated mitral valve prolapse with mild-to-moderate mitral regurgitation, trivial tricuspid regurgitation, and top normal aortic root dimension (z-score +1.7). Chest X-ray and electrocardiogram were normal. The DNA sequence analysis of *FBN1* identified a heterozygous missense pathogenic variant in *FBN1*: c.3037G > A (p. Gly1013Arg) in exon 24. The variant is considered strongly pathogenic based on American College of Medical Genetics classification. Genetic testing on parents was not performed due to financial constraints. A de novo pathogenic variant was suspected as the family history was negative for physical features suggestive of MFS.

Her cardiovascular course in her first 12 years of life is as follows. She developed clinical features of CHF due to progressive severe mitral valve insufficiency, at 4 months of age. A follow-up echocardiogram at 4 months showed severe mitral regurgitation, mild tricuspid regurgitation, dilated left ventricle with normal biventricular systolic function, and dilated aortic root (z-score +2.9) with no aortic regurgitation. Patient was initially managed with medications for CHF: digoxin and furosemide, along with atenolol for the aortic root dilatation. Losartan was subsequently added at 1 year of age, in view of severe progressive aortic root dilatation during follow-up. With time, she developed progressive CHF unresponsive to medical management. She, therefore, underwent mitral valve replacement with a bileaflet mechanical St Jude prosthetic valve at 4.5 years of age. Subsequent to the mitral valve replacement, she improved clinically and had resolution of the CHF symptoms and the left ventricular dilatation. She continues to have severe aortic root dilatation without any aortic valve insufficiency. Her aortic root dimension has been stable over the past 2 years, but it is anticipated that she will eventually need aortic root repair/replacement. ► **Fig. 1** is a graphical representation of her progressive aortic root and left ventricular diastolic dimensions over time.

She developed bilateral lenticular dislocation at 1 year of age. She had progressive high myopia with refractory amblyopia and astigmatism. These are being managed currently with corrective lenses and are being followed closely by ophthalmology. She developed worsening pectus and severe progressive scoliosis (46° Cobb angle), causing severely restricted pulmonary function with forced expiratory volume in one second (FEV1) of 37% predicted, forced vital capacity (FVC) of 48%, and FEV1 to FVC ratio of 0.8. In

Fig. 1 Graph showing aortic root dimension and left ventricular end diastolic diameter z-scores over time in patient 1.

view of this, she underwent surgical correction of her scoliosis at 7 years of age with Harrington rod placement. Following scoliosis repair, her pulmonary function improved with amelioration of the restrictive pulmonary physiology. She is currently asymptomatic from the cardiopulmonary standpoint and is being closely monitored in a multidisciplinary setting. She is attaining all developmental milestones without evidence of cognitive deficiency.

Patient 2

Patient 2 is a 9-year-old female patient who was diagnosed to have infantile form of MFS at 9 months of age. She was born as the first child of healthy nonconsanguineous parents. She had been attaining her developmental milestones appropriately. She initially presented at 6 months of age to the ophthalmologist with high myopia and megalocornea, when she was noted to have MFS phenotype and was referred to the geneticist. During the genetic evaluation, she was noted to have dysmorphic features including tall stature (length > 99th percentile), deep set eyes with prominent forehead, large

protruding ears, senile facial appearance, arachnodactyly, long and thin extremities with hyperflexible joints, and pectus carinatum. Targeted genetic testing demonstrated a heterozygous missense variant in *FBN1*: c.3661T > C (p. Cys1221Arg) in exon 29. This variant is classified as a variant of unknown significance in ClinVar. This is the first reported case of this mutation with early-onset Marfan phenotype. The mother had genetic testing for this *FBN1* pathogenic variant and was found to be negative. The father declined to have the genetic testing. A de novo pathogenic variant was suspected as the family history was negative for physical features suggestive of MFS. Initial cardiac evaluation at 9 months age in this child revealed mitral valve prolapse resulting in moderate degree of mitral regurgitation, tricuspid valve prolapse with moderate degree of regurgitation, and severe aortic root dilatation (z-score of +4) without any aortic valve insufficiency. She was started on digoxin, losartan, and atenolol in view of significant mitral insufficiency and aortic dilatation. She was closely followed, and in view of progressively severe left ventricular dilatation due to the mitral insufficiency and severe aortic root dilatation, she underwent bioprosthetic mitral valve replacement along with aortic root and ascending aorta sleeve placement surgery at the age of 6. Currently, her cardiac condition is stable, and is closely followed by the multidisciplinary team.

With regard to her eyes, she developed iridodonesis, phacodonesis, bilateral lens dislocations, and progressive myopia with refractory amblyopia for which she is wearing corrective lenses and is being followed by the ophthalmologist. She also has moderate degree (37° Cobb angle) of scoliosis and spirometry was attempted, but she was unable to produce reproducible maneuvers. Her scoliosis is being currently managed with a spinal brace since 5 years age. She was found to have a cyst in her spine by a magnetic resonance imaging exam and is being closely monitored by orthopedics for this.

Patient 3

Patient 3 is a 5-year-old girl who was born full term to healthy nonconsanguineous parents via normal vaginal delivery after an uneventful pregnancy and delivery. She had been attaining her developmental milestones appropriately. At 3 years of age, during routine pediatric clinic visit, she was noted to have tall stature along with dysmorphic features. She was referred for genetic evaluation in view of multiple physical features suggestive of MFS. At the time of initial presentation, she had the following features: severe myopia, dislocated lens, scoliosis, tall stature (height >99th percentile), pes planus, and pectus carinatum deformity of the chest. Other dysmorphic features noted include high arched palate, long face, deep-set eyes, retrognathia, and arachnodactyly, with Ghent score of 9. Cardiac examination revealed a mid-systolic click and a grade 2/6 mid-to-late systolic murmur heard best at the apex, consistent with mitral valve prolapse. Initial echocardiogram demonstrated moderate degree of prolapse of anterior and posterior mitral valve leaflets with mild mitral regurgitation, mild prolapse of tricuspid valve leaflets with mild tricuspid regurgitation,

severe aortic root dilatation measuring 3.3 cm (z-score of +6) with trivial aortic insufficiency, mild dilatation of the ascending aorta (z-score of +2.8), along with moderate dilatation of the main pulmonary artery (z-score of +4.2). She was started on atenolol during her initial cardiology evaluation.

Targeted genetic testing demonstrated a heterozygous missense pathogenic variant in *FBN1*: c.3557 A > G (p. Tyr1186Cys) in exon 29. This variant is classified as a variant of unknown significance in ClinVar. This is the first reported case of this mutation with early-onset Marfan phenotype and is therefore considered possibly pathogenic. The level of evidence is “moderate pathogenicity” based on the American College of Medical Genetics classification. The parents declined to have genetic testing done on them. A de novo pathogenic variant was suspected as neither parent had physical features of MFS. During a most recent evaluation at 5 years of age, she has bilateral lenticular dislocation with severe myopia for which she is wearing corrective lenses. She has mild scoliosis (19° Cobb angle) which is being treated with a corrective brace. Spirometry was attempted but she was unable to produce reproducible maneuvers. The severity of mitral valve insufficiency has worsened with time from mild during her initial presentation to a moderate degree at her 5-year-visit. The most recent echocardiogram still showed normal left ventricular diastolic dimension. The aortic root dimension is stable while on atenolol (z-score of +5.8). Mitral valve replacement will be considered in the future, if there is progressive worsening of mitral insufficiency, leading to severe left ventricular dilatation and/or development of clinical features of CHF, refractory to medical management. She is being followed by a multidisciplinary team.

Discussion

MFS is an autosomal dominant connective tissue disorder with abnormalities primarily involving musculoskeletal, ocular, and cardiac structures.⁷ The revised Ghent criteria are the most recently proposed nosology for the diagnosis of MFS. According to this nosology, any patient fulfilling certain combination of aortic dilation, ectopia lentis, systemic features, family history, and *FBN1* pathogenic variant can be diagnosed with MFS.¹¹

Early-onset MFS is a rare subset with phenotypic expression of the various abnormalities occurring in neonatal or infantile period.¹² However, there are both genotypic and phenotypic differences between early-onset and classical MFS (–Table 1). Although both are autosomal dominant, classical MFS occurs sporadically in only approximately 25% of cases, whereas the early-onset variety is more frequently sporadic. This presumably leads to the severity of the condition with high lethality prior to reaching adulthood or child-bearing age. Although pathogenic variants in classical MFS have been observed along the entire length of *FBN1*, pathogenic variants in early-onset MFS tend to cluster in a relatively small region of *FBN1*, approximately between the exons 24 and 32. Previous studies demonstrated that, even if the exons 24 to 32 location appear as a major cause of the

Table 1 Comparison between early-onset Marfan syndrome and classical Marfan syndrome

Characteristics	Early-onset Marfan syndrome	Classical Marfan syndrome
Clinical characteristics		
Age at death	Less than 2 years	Comparable to general population
Main cause of death ¹	Congestive heart failure	Aortic dissection or rupture
Family history of Marfan syndrome	Negative in 70–100%	Negative in 20–30%
Joint contractures	47–64%	Uncommon
Cardiovascular characteristics		
Mitral valve prolapse	73–100%	60–90%
Mitral regurgitation	89%	13%
Aortic dilation	80–100%	60–85%
Aortic regurgitation	11%	73%
Tricuspid regurgitation	67%	Uncommon
Pulmonary regurgitation	22%	Uncommon

severity of the phenotype in patients with a mutation in this region, other factors such as the type of mutation or modifier genes might also be relevant.^{13,14} Loeys et al in 2001 reported a large series of patients with MFS, in which the authors found a mix of mostly missense and nonsense mutations. In that series, most reported mutations in the “hotspot” region were missense.¹⁵ The genotype described in patient 1 has been previously reported as a disease-causing pathogenic variant in two patients by Tiecke et al. The first patient in that report was diagnosed with early-onset MFS at 8 months of age and subsequently underwent prophylactic aortic valve replacement with homograft replacement of the ascending aorta. That patient died suddenly 1 week following surgery due to suture dehiscence and internal hemorrhage. The second patient was diagnosed at a few months of age and subsequently underwent mitral valve graft with remodeling of the aortic valve and ascending aorta at the age of 3 years.²

The primary cause of death in classical MFS is aortic root disease in the form of aortic dissection or rupture of an ascending aortic aneurysm,¹⁶ but the predominant mode of death in the early-onset form is cardiac failure secondary to a severely regurgitant mitral valve.^{17–19} With adequate monitoring and timely interventions along with advances in the surgical management techniques, more patients with early-onset MFS live longer. The prognosis of early-onset MFS is historically poor. In a meta-analysis of 86 patients with early-onset MFS, Strigl et al noted the mean age of death as 16.3 months in their patient population.²⁰

Medical therapy of heart failure from chronic severe mitral regurgitation is often reported to be unsuccessful to control the symptoms.²¹ Surgical repair of the mitral valve in MFS is often difficult due to severe myxomatous changes in the valve leaflets. Therefore, mitral valve replacement is the only option for those with severe heart failure which is refractory to medical management.⁸ However, until ~15 years ago, this operation was associated with higher mortality and morbidity including complete heart

block, thrombosis, and stroke.^{3,5} In recent years, with improved surgical techniques, cardiopulmonary bypass methods, newer mechanical valves, and tissue derived bioprosthetic valves, increasing number of young children with early-onset MFS are surviving mitral valve replacement surgeries, as noted in our cohort. Indications for mitral valve replacement following established guidelines include symptomatic mitral regurgitation, or asymptomatic patients with one or more of the following features: severe left ventricular enlargement with end systolic diameter of the left ventricle exceeding 4 cm, left ventricular systolic dysfunction, secondary pulmonary hypertension, or development of new onset atrial fibrillation.²²

Aortic dilatation-related complications are the next most common cardiovascular manifestation in early-onset MFS. Progressive aortic root dilatation could lead to aortic regurgitation and aortic dissection. Medical therapy with beta blockers has been the standard form of treatment in classical MFS, in an attempt to slow the rate of aortic root dilatation by reducing the hemodynamic stress on the aorta. More recently, angiotensin II receptor blockers have been used in MFS. It acts by antagonism of TGF- β , thereby targeting the underlying pathophysiology of MFS. It has been proven to be effective as monotherapy in reducing the rate of progression of aortic root in classical MFS.²¹ Clinical trials are ongoing to assess the efficacy of combination therapy in reducing the rate of aortic dilatation in classical MFS. Currently, there is paucity of data in the ideal medical regimen for the management of early-onset MFS, due to the rarity of its diagnosis. Aortic dilatation-related complications tend to occur in adults when the aortic root diameter exceeds 60 mm in classical MFS. Consequently, elective aortic root replacement is indicated when the aortic root dimension exceeds 50 mm in adults with MFS. However, in early-onset MFS, the decision for aortic root replacement should rather be individualized based on the rate of progression of the aortic root dilatation.²³ In addition to the cardiovascular differences, the early-onset form of MFS has a higher incidence of scoliosis (32%) than classical MFS. Bracing is

recommended for skeletally immature patients whose Cobb angle is 30 to 39° at the time of presentation. Surgical correction is indicated for skeletally immature patients whose Cobb angle is $\geq 50^\circ$.²⁴ Early-onset MFS is also reported to have considerable morbidity due to joint contractures (67%) and recurrent joint dislocations (36%).²⁵ This group, therefore, has higher morbidity and mortality rates when compared with classical MFS. In our present patient series with early-onset MFS, the clinical evolution has been remarkably positive considering other pediatric cases described in the literature, possibly due to more aggressive medical and timely surgical interventions.

In summary, early-onset MFS referred to as the infantile variety by some authors is associated with potentially lethal cardiovascular manifestations early in life. Over the past two decades, with improvements in the multidisciplinary approach to this patient population, including timely cardiovascular and scoliosis surgical managements, the outlook for this subgroup has substantially improved, with more of these patients reaching adult age.

Funding
None.

Financial Disclosure
All the authors have no financial relationships relevant to this manuscript to disclose.

Conflict of Interest
None declared.

Acknowledgments
The authors thank the patient's families for their participation in this reporting.

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