Clinical Vignette

Early Onset Marfan Syndrome in a Neonate with a Novel Pathogenic Variant in the Non-Hotspot Region of the *FBN1* Gene

Gayatri Nerakh[1], Bhargavi Dhulipudi[2], Sai Kiran Deshabhotla[3]

1 Department of Fetal Medicine and Medical Genetics, Fernandez Foundation, Hyderabad, Telangana, India
2 Department of Cardiology, Rainbow Children Heart Institute, Hyderabad, Telangana, India
3 Department of Neonatology, Fernandez Foundation, Hyderabad, Telangana, India
Correspondence to: Dr Gayatri Nerakh. Email: maildrgayatri@gmail.com

Abstract

Early onset Marfan syndrome (eoMFS) is a rare form of classic Marfan syndrome. It is distinct from the classic Marfan syndrome in severity. The present case report is of a neonate with increased length, facial dysmorphism and arachnodactyly without any joint contractures. On transthoracic echocardiography (TTE) there was annulo-aortic ectasia. Exome sequencing revealed a de novo novel splice site pathogenic variant c.4336+2T>C in intron 35 of the *FBN1* gene. The child was started on beta blocker therapy. On follow up, the child developed progressive increment in aortic root dimension with new onset mild aortic regurgitation and mitral regurgitation. Beta blocker was stopped and angiotensin receptor blocker (ARB) was started. The child responded well with ARB and kept on medical follow up. The current case highlights that the identification of more novel variants in non-hotspot regions of the *FBN1* gene would help in understanding the genotype-phenotype correlations in eoMFS. This case also highlights the relevance of timely molecular diagnosis which helps in appropriate management and prognostication in such a scenario.

Keywords: Early onset Marfan syndrome, *FBN1* gene, Fibrillinopathy

Patient details

This term female neonate was the first offspring of a healthy non-consanguineous couple. Detailed fetal anomaly scan showed bilateral choroid plexus cysts. Polyhydramnios was noted from 28 weeks. The baby was born by Cesarean delivery with a birth weight of 3.3 kg. On examination at birth, the length was 52cm (90th centile), head circumference was 36cm (95th centile) and weight was 3.3kg (70th centile). Arm span to length ratio was 1.07 and upper segment to lower segment ratio was 1.6. There was relative macrocephaly, sparse hair over the frontal region, depressed nasal bridge, deep-set eyes, down slanting of palpebral fissures, malar hypoplasia, high arched palate, and prominent chin (**Figure 1a**). The neck and spine were normal. Chest showed slight pectus excavatum. Extremities were long with long fingers (**Figure 1b**), toes and pes planus (**Figure 1c**). There were no contractures/joint dislocations. Central nervous system and per abdominal examination was unremarkable. On auscultation, there was non-ejection click and 2/6 ejection systolic murmur. Transthoracic echocardiography (TTE) at birth showed annulo-aortic ectasia with aortic root Z score of +2.4 (**Figures 2a, 2b, 2c, 2d**). Ophthalmological examination and hearing evaluation were normal. Bilateral choroid plexus cysts were noted on neurosonogram. Infantogram, ultrasound abdomen and extended newborn screening were normal. There was no family history of tall stature, sudden cardiac deaths or loss of vision. Parents were normal on clinical examination. Marfan syndrome was suspected and whole exome sequencing was done.

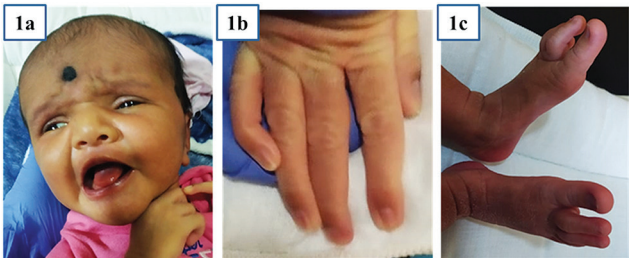

Figure 1 **Clinical features of the child**
1a. Craniofacial dysmorphism in the form of relative macrocephaly, sparse hair over the frontal region, depressed nasal bridge, deep-set small eyes with down slant of palpebral fissures, malar hypoplasia, and prominent chin
1b. Long fingers
1c. Pes planus with long toes

Whole exome sequencing of the child revealed a novel heterozygous pathogenic variant c.4336+2T>C (5' splice site) in intron 35 of the *FBN1* gene. The variant is not present in population databases. Classification of the variant is 'pathogenic' as per the American College of Medical Genetics and Genomics and the Association for Molecular

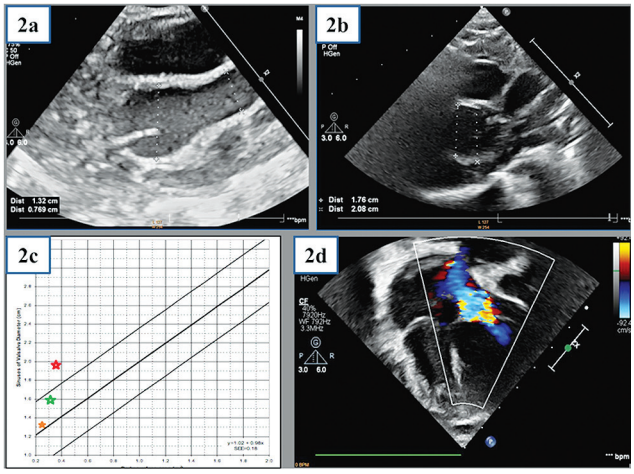

Figure 2 **2D Echocardiography findings**
2a. Transthoracic echocardiography (TTE) in the parasternal long axis (PLAX) view at birth showed aortic root dilatation of 13mm (Z score +2.4)
2b. TTE image in PLAX view at 7 months of age showed progressive aortic root dilatation of 20 mm(Z Score+7.2).
2c. Graph showing progressive dilatation of the sinus of Valsalva (aortic root) from birth till the age of 1.5 years.
2d. TTE image showing apical 4 chamber view with color integration at mitral valve showing moderate mitral valve regurgitation.

Pathology (ACMG/AMP) variant classification guidelines. In-silico databases predicted the variant to be 'disease-causing' due to dysregulation of splicing. The residue at which the change occurred in the fibrillin protein is well conserved throughout evolution. Targeted testing of the couple revealed absence of the variant in them.

Initially the child was started on beta blocker therapy. As there was progressive dilatation of the aortic root (Z score +7.2) with new onset aortic and mitral valve regurgitation, beta blocker was stopped, and angiotensin receptor blocker (ARB) was started. Parents were counseled regarding future need of aortic and mitral valve surgery. At present, the child is 21 months old and is stable.

Discussion

Fibrillinopathies are a group of connective tissue disorders. Early onset Marfan syndrome (eoMFS), a fibrillinopathy, differs from classical Marfan syndrome in the clinical presentation and severity. EoMFS is more frequently sporadic (Hennekam et al., 2005). Modified Ghent criteria is used for diagnosis of early onset Marfan syndrome. These children present with senile facial appearance, ectopia lentis, arachnodactyly, scoliosis, joint contractures/dislocations, and cardiac involvement. Our patient did not have scoliosis or joint contractures/dislocations. Aortic root involvement is less common than valvular insufficiency and even if aortic dilatation occurs, dissection is quite rare (Stheneur et al., 2011). Aortic valvular insufficiency is less frequent but, in this child, aortic regurgitation was present. Those with valvular insufficiency had shorter life expectancy. The average age of death is reported as 16 months (Loeys et al., 2010).

Pathogenic variants in the *FBN1* gene can lead to mild to severe phenotype like mild skeletal abnormalities to the severe cardiac phenotype. Variants in early onset form of classic Marfan syndrome are located in exons 24-32 of the *FBN1* gene (hot spot region). Most of them are missense variants. This hot spot region encodes eight calcium-binding epidermal growth factor-like (cbEGF) domains with six conserved cysteine residues (Tiecke et al., 2001; Abdel-Massih et al., 2002). Substitutions of one of these cysteine residues disrupt the disulphide bond leading to misfolding of the domain, deleterious effects on the structure of fibrillin-1 protein, enhanced susceptibility of fibrillin for proteases, and interference with heparin binding which play a critical role in microfibril assembly (Haller et al., 2020; Matyas et al., 2007). Our case had a novel 5' splice site variant in intron 35 of the *FBN1* gene which is not in the hot spot region but is associated with a severe cardiac phenotype. This could be because of the effect of modifier genes (Faivre et al., 2009).

Neonatal Marfan syndrome (nMFS) is the differential diagnosis considered for this child. nMFS presents with cardiac failure in the early infantile period and they succumb by the age of 2 years. The average age of death in eoMFS is the adolescent period (Hennekam et al., 2005). Exact labeling of these patients would therefore help in appropriate counseling and more accurate prognostication.

Beta blockers are used to prevent and treat MFS patients including eoMFS. Recent studies have shown that ARBs are beneficial in patients with significant aortic root dilatation and mitral valve regurgitation (Strigl et al., 2007). Patients with congestive heart failure and severe aortic

regurgitation need aortic valve replacement, quadrivalve replacement or heart transplantation. Aortic root surgeries are recommended in cases with rapid progression of aortic diameter (>5mm/ year) or if aortic diameter is ≥ 45 mm (Takeda et al., 2016). Any surgical intervention in an infant is associated with significant morbidity and mortality. Early diagnosis and initiation of medical therapy helps in delaying the surgical intervention (Ardhanari et al., 2019). Treatment of early onset Marfan syndrome is still challenging even in patients with early diagnosis as there is no clear data on ideal medical management. In our case, the child was clinically stable on medical management at the age of 21 months.

Conclusion

This is the first reported patient of early onset Marfan syndrome with a pathogenic variant outside the non-hotspot region of the *FBN1* gene. Identification of new variants in non-hotspot regions and other genetic modifiers would help in clear understanding of the genotype–phenotype correlations of these patients.

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