Successful Mitral Valve Replacement in an Infant with Neonatal Marfan Syndrome due to a Novel Missense Mutation of the \textit{FBN1} Gene

A Case Report and Review of Literature

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Summary

Marfan syndrome is an autosomal dominant genetic disorder of the fibrous connective tissue caused by pathogenic mutations in the fibrillin-1 gene. Neonatal Marfan syndrome is a rare type of Marfan syndrome that is genotypically and phenotypically different from classical Marfan syndrome and has a poor prognosis. Most patients with neonatal Marfan syndrome die during infancy due to severe and rapidly progressive cardiovascular disorders. Here, we present a case of an 11-year-old girl with neonatal Marfan syndrome due to a novel missense mutation in exon 27 of the fibrillin-1 gene. Her condition was critical due to progressive mitral and tricuspid regurgitation. Mitral valve replacement, performed at the age of 6 months, improved her critical condition. Our case suggests that early mitral valve replacement may lead to better outcomes in patients with neonatal Marfan syndrome.

\textit{Key words:} Congenital heart disease, Early intervention, Long-term survival, Valvuloplasty

\textbf{M}arfan syndrome (MFS; OMIM: 154700) is an autosomal dominant disorder of the fibrous connective tissue caused by pathogenic mutations in the fibrillin-1 \textit{(FBN1)} gene. MFS is characterized by ocular, skeletal, and cardiovascular manifestations.\textsuperscript{11} Among these manifestations, cardiovascular insufficiency is associated with early mortality.\textsuperscript{12} The timing of onset and symptom severity differ among cases. Moreover, MFS is classified as classical MFS or neonatal MFS (nMFS).

nMFS is a rare condition occurring \textless{} 100 cases reported in the literature. Its presentation is the most severe in early childhood.\textsuperscript{13} nMFS results in external malformations and rapid progression of cardiopulmonary dysfunction from early infancy.\textsuperscript{14} Most patients with nMFS die within the first year of life, with a median survival of 16.3 months.\textsuperscript{15} Valvular insufficiencies and diaphragmatic hernias have been associated with short survival in patients diagnosed during infancy.\textsuperscript{16}

Here, we present a case of an 11-year-old girl with nMFS who had a novel missense mutation in exon 27 of \textit{FBN1}. She had severe mitral regurgitation (MR) during the neonatal period. Mitral valve replacement (MVR) using a mechanical valve was successfully performed at 6 months of age, and the patient was doing well at the last follow-up. Early valvular intervention may lead to a good prognosis in patients with nMFS.

\textbf{Case Report}

A Japanese female infant was born at 40 weeks of gestation \textit{via} vaginal delivery. She had no family history of genetic disorders, including MFS, aortic diseases, or sudden death. Her birth body weight and height were 3,008 g (−0.2 standard deviation [SD]) and 50.1 cm (+0.2 SD), respectively. The Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. She was admitted to the neonatal intensive care unit (NICU) soon after birth due to heart murmur and respiratory disorder. She had dysmorphic features characterized by senile facial appearance, arachnodactyly, wrist and thumb sign, and flatfoot (Figure 1). Echocardiography revealed mitral valve prolapse, moderate MR, and aortic root dilatation. She did not have any ophthalmologic complications. Based on the clinical findings, the patient was diagnosed with nMFS. Diuretics were initiated, and she was discharged from the NICU 24 days after birth. At 3 months of age, she exhibited respira-
tory distress, poor sucking, and weight gain. Echocardiography revealed significant dilatation of the left ventricle (35.3 mm, Z-score, +6.7) and the aortic sinus (15.8 mm, Z-score, +3.2) and massive MR. Therefore, oral losartan was initiated. At 5 months of age, echocardiography revealed enlargement of the mitral annulus diameter (22.1 mm, Z-score +3.0), grade IV MR, and tricuspid regurgitation (TR) (Figure 2). Cardiac catheterization at 5 months of age revealed an increased left ventricular end-diastolic volume of 40.9 mL (215% of normal) with a cardiac output of 2.16 L/minute and a markedly dilated aortic sinus (20.1 mm, Z-score +6.2 mm). Given these findings, a decision was made to perform surgical intervention on the mitral and tricuspid valves. During the operation, we observed that the mitral leaflets were thickened, myxoid, and degenerative, the chordae were elongated, and the annulus of the valve was dilated. The mitral valve was similar in presentation to Barlow’s mitral valve disease. After discussion with the surgical team, we decided to perform MVR but not mitral valvuloplasty as they speculated that mitral valve prolapse and severe MR might have occurred soon after surgery. Therefore, she underwent MVR with the use of a 21-mm SJM-Regent valve (St. Jude Medical Inc., Minneapolis, MN, USA). In addition to the mitral valve, we observed dysplastic changes in the tricuspid valve. These changes were milder compared with those in the mitral valve. Hence, valvuloplasty was performed on the tricuspid valve. Subsequently, MR disappeared and LV dilatation improved to 33.8 mm (Z-score, +3.1). TR also decreased to a trivial level. The aortic sinus enlargement gradually progressed after the surgery: 25.2 mm (Z-score: +3.12) without aortic regurgitation (AR) at 6 months, 27.3 mm (Z-score: +8.66) without AR at 1 year and 3 months, 34.8 mm (Z-score: +11.26) with trivial AR at 3 years and 10 months, 42.0 mm (Z-score: +12.6) with trivial AR at 5 years and 3 months, and 46.0 mm (Z-score: +14.6) with trivial AR at 8 years and 10 months after the surgery. Her body weight gradually improved from 3,008 g (−2.0 SD) to 8,060 g (−0.8 SD) at 1 year of age. At the last follow-up, the patient was 11 years old and did not need reoperation; she had been living an independent life and had adequate neuropsychomotor development for her age.

**Molecular studies:** At 17 months of age, the patient underwent genetic analysis, which revealed a novel mutation in *FBN1* with a heterozygous missense variant in exon 27 (c.3379G>T) (Figure 3A). This mutation results in the substitution of cysteine with glycine in the 13th calcium-binding epidermal growth factor-like (cbEGF) domain of the FBN1 protein. The patient’s parents did not have the same mutation (Figure 3B and C). This mutation in *FBN1* has not been reported in the UMD-FBN1 mutation database, which has registered 80 mutations associated with nMFS (http://www.umd.be/).

**Literature review:** We reviewed all reported cases of nMFS who underwent cardiac surgery in the Medline and Embase databases. The key terms used in the search were “neonatal Marfan syndrome,” “early-onset Marfan syndrome,” or “rapidly progressive Marfan syndrome.” We found a total of 20 cases that have been reported in 16 studies. Various surgical procedures such as mitral valvuloplasty (31%), MVR (26%), mitral annul-
Figure 3. Mutation analysis showing a novel missense mutation in exon 27. A: Sequence analysis in the patient. There is a G > T transition (arrow) resulting in a glycine to cysteine substitution within one of the calcium-binding epidermal growth factor-like domains. B, C: Sequence analysis in the patient’s parents. The same mutation is not present in the parents.

Table. Summary of Patients with Neonatal Marfan Syndrome Who Underwent Surgical Intervention

| Author          | Journal          | Year | Sex | Exon | Nucleotide change                | Age and status at the last follow-up | Cardiac surgery  | Operated age |
|-----------------|------------------|------|-----|------|----------------------------------|--------------------------------------|------------------|--------------|
| Whitelaw CM, et al. | Am J Med Genet | 2004 | F   | 25   | c.3202T > C c.3204C > G          | 11 weeks dead                        | MVP              | 11 weeks     |
|                 |                  |      |     |      |                                  |                                      | MVR aortic surgery | 13 months    |
| Ter Heide H, et al. | Clin Dysmorphol | 2005 | M   | 29   | c.3706T > C                      | 4 years alive                        | MVP              | 6 months     |
|                 |                  |      |     |      |                                  |                                      | MVR              | 8 months     |
| Ramaswamy P, et al. | Pediatr Cardiol | 2006 | M   | ND   | ND                               | 15 months alive                      | MVR              | 10.5 months  |
| Beroukhim RS, et al. | Pediatr Cardiol | 2006 | M   | ND   | ND                               | 3 years alive                        | MVP              | 29 months    |
| Brito-Filho SL, et al. | Cardiol Young | 2013 | F   | ND   | ND                               | 11 years alive                       | Bentall          | 2 years, 4 years, 7 years |
| Buchhorn R, et al. | Open J Thorac Surg | 2014 | F   | ND   | ND                               | 10 months dead                       | MVP TVR          | 7 months     |
| Amado M, et al. | BMJ Case Rep     | 2014 | F   | 27   | c.3458G > A                       | 34 months alive                      | MVP              | 6 months     |
| Kitahara H, et al. | Ann Thorac Surg | 2016 | M   | ND   | ND                               | 11 years alive                       | MVP              | 18 months    |
|                 |                  |      |     |      |                                  |                                      | MVR              | 3 years      |
| Maeda J, et al. | Heart Vessels    | 2016 | M   | 26   | c.3217 G > A                      | 10 years alive                       | MVP              | 18 months    |
|                 |                  |      |     |      |                                  |                                      | VSRR MAP         | 29 months    |
| Le Gloan L, et al. | Mol Syndrome    | 2016 | F   | 49   | c.IVS29 + 1 G > A                 | 22 months dead                       | MAP TAP          | 5 months     |
| Heo JS, et al. | J Korean Med Sci | 2017 | M   | 26   | c.3276 G > A                      | ND ND repair of MCTR                 | MVP              | 1 year       |
| Carande EJ, et al. | Case Rep Pediatr | 2017 | F   | 26   | c.3143T > C                       | 14 months alive                      | MVP TVP          | 11 months    |
| Ardhana M, et al. | J Pediatr Genet | 2019 | F   | 24   | c.3037 G > A                      | 12 years alive                       | MVP              | 4.5 years    |
|                 |                  |      |     |      |                                  |                                      | MVR              | 6 years      |
| Tognato E, et al. | Am J Perinatol  | 2019 | M   | 25   | c.3143T > C                       | 13 months alive                      | MVP TVP          | 11 months    |
| Cua CL, et al. | Ann Thorac Surg | 2020 | ND  | 28   | c.3476 G > A                      | 29 months alive                      | MVP              | 10 months    |
| Kawamura J, et al. | Cardiol Young   | 2022 | M   | 29   | c.3706T > C                       | 13 months alive                      | MVP TVP          | 6 months     |
|                 |                  |      |     |      |                                  |                                      | VSRR MAP         | 7 months     |
| Present case    |                  |      |     | 27   | c.3379 G > T                      | 11 years alive                       | MVP TVP          | 6 months     |

MAP indicates mitral annuloplasty; MCTR, mitral chordae tendineae rupture; MVP, mitral valvuloplasty; MVR, mitral valve replacement; ND, not described; TAP, tricuspid annuloplasty; TVP, tricuspid valvuloplasty; TVR, tricuspid valve replacement; and VSRR, valve sparing aortic root replacement.
lloplasty (11%), tricuspid annuloplasty (9%), tricuspid valve replacement (6%), valve-sparing aortic root replacement (3%), Bentall procedure (3%), and repair of mitral chordae tendineae rupture (3%) were performed in these cases. In these cases, 11 (55%) patients were female, and the average age at surgery was 20 months (range, 1 month to 7 years). At the last follow-up, 13 patients (65%) were alive. The average postoperative survival time was 25 months (range: 1 month to 8 years).

Discussion

Here, we report the youngest case of nMFS who underwent MVR. The follow-up reported in our case is also the longest so far. Epigenetic analysis revealed a novel de novo mutation in FBN1. Although our patient was critically ill during infancy due to her cardiac conditions, early surgical intervention, including MVR, may have improved the prognosis.

It is difficult to perform MVR in the pediatric population due to various problems, such as unsuitable mechanical valve size or bleeding events related to the use of oral warfarin.22 However, considering the rapid progression of cardiovascular involvement and high mortality, early intervention at the optimal age could improve the prognosis of nMFS. According to our literature review, MVR has been increasingly performed in recent years, and it appears to be associated with long-term survival. Although MVR in early infancy is often challenging, recent improvements in surgical techniques and devices have improved its surgical performance.24 Children with MFS generally exhibit average intellectual and gross motor development.25 In our patient, neurological development was consistent with that reported in a previous report.26 Considering the aforementioned viewpoints, early MVR for lifetime extension may be a worthwhile strategy for patients with nMFS, regardless of its difficulty.

Another concern in our case was a novel de novo mutation in FBN1. Approximately 25% of patients with MFS exhibit de novo mutation(s) in FBN1, which is located on chromosome 15q21.1.2 FBN1 mutations associated with MFS are known to exist between exons 24 and 32, which is the neonatal region of FBN1.11 This region is predominantly composed of eight calcium-binding epidermal growth factor-like (cbEGF) domains (cbEGF1-cbEGF18), each of which binds one calcium ion and is stabilized by three highly conserved disulfide bounds.26 In our case, a novel mutation was observed in exon 27 of FBN1 (c.3379G>T). The mutation resulted in the substitution of cysteine with glycine at codon 1127 (p.Gly1127Cys) in the 13th cbEGF domain of the FBN1 protein. Mutations in the cbEGF domain are presumed to interfere with calcium binding. Calcium plays a significant role in the stabilization of the cbEGF domains. As a result, perturbed calcium binding caused by the cbEGF domain mutation is thought to be a central driver of nMFS pathophysiology.26 According to a previous report, a change in the 13th cbEGF domain has a lesser conformational effect on the FBN1 protein compared with other cbEGF domains. Whiteman, et al. demonstrated that (1) covalent linkage of cbEGF12 preserves the native-like fold of cbEGF13 G1127S and that (2) conformational effects introduced by G1127S are localized to cbEGF. The structural change was less impacted by the G1127S mutation in cbEGF13 and more impacted by the E1073K mutation in cbEGF12.21 We speculate that the difference in the sites of mutation domains affects the range of structural effects followed by favorable prognosis in the present case.

In conclusion, our case suggests that early MVR can improve the prognosis of nMFS in terms of survival. Hence, surgical interventions should be considered at the optimal timing. Further studies are needed to evaluate the efficacy and feasibility of early valvular interventions in patients with nMFS.

Disclosure

Conflicts of interest: There are no conflicts of interest to declare.

Informed consent: Written informed consents were obtained from the patients’ parents.

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