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Infantile Marfan syndrome in a Korean tertiary referral center

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Purpose: Infantile Marfan syndrome (MFS) is a rare congenital inheritable connective tissue disorder with poor prognosis. This study aimed to evaluate the cardiovascular manifestations and overall prognosis of infantile MFS diagnosed in a tertiary referral center in Korea.
Methods: Eight patients diagnosed with infantile MFS between 2004 and 2014 were retrospectively evaluated.
Results: Their median age at the time of diagnosis was 2.5 months (range, 0–20 months). The median follow-up period was 25.5 months (range, 0–94 months). The median length at birth was 50.0 cm (range, 48–53 cm); however, height became more prominent over time, and the patients were taller than the 97th percentile at the time of the study. None of the patients had any relevant family history. Four of the 5 patients who underwent DNA sequencing had a fibrillin 1 gene mutation. All the patients with echocardiographic data of the aortic root had a *z* score of >2. All had mitral and tricuspid valve prolapse, and various degrees of mitral and tricuspid regurgitation. Five patients underwent open-heart surgery, including mitral valve replacement, of whom two required multiple operations. The median age at mitral valve replacement was 28.5 months (range, 5–69 months). Seven patients showed congestive heart failure before surgery or during follow-up, and required multiple anti-heart failure medications. Four patients died of heart failure at a median age of 12 months.
Conclusion: The prognosis of infantile MFS is poor; thus, early diagnosis and timely cautious treatment are essential to prevent further morbidity and mortality.

Key words: Marfan syndrome, Mitral valve insufficiency, Newborn infant

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Introduction

Marfan syndrome (MFS) is a multisystemic disorder of connective tissue inherited in an autosomal dominant fashion[1]. It is caused by mutations in the extracellular matrix protein fibrillin1[2]. Current diagnostic manifestations include skeletal, ocular, cardiovascular, pulmonary, cutaneous, and central nervous system abnormalities as well as a family history[3,4]. There have been numerous case reports of MFS in infancy; however, infantile MFS is still rarely diagnosed at younger ages, because morphological characteristics of the syndrome are age-dependent, phenotypic variability is remarkable, and most patients show *de novo* mutations[3]. Cardiovascular abnormalities are the major cause of death in infantile MFS, and the most common presenting findings are mitral and/or tricuspid valve regurgitation, which is less common in classic MFS[5,6]. Long-term follow-up and proper management including open-heart surgery in a timely manner would have beneficial effects on the prognosis of the patients. However, little is known about infantile MFS in South Korea. The aim of this study was to evaluate cardiovascular manifestations and the overall prognosis of recently diagnosed cases of infantile MFS in a tertiary referral center

Table 1. Clinical findings of the patients with infantile Marfan syndrome

Case	Sex	At birth		At diagnosis	Presenting symptom	Follow-up period (mo)	At the time of study			Mortality
		Body weight kg (percentile)	Height cm (percentile)	Age (mo)			Age (mo)	Body weight (kg, percentile)	Height (cm, percentile)	
1	F	3.48 (50–75)	NA	12	Cannot stand up alone at 12 mo	94	130	32.5 (25–50)	159.6 (>97)	Expired
2	F	2.5 (<3)	NA	8	Murmur	39	47	12.6 (<3)	88.5 (10–25)	Alive
3	F	3.35 (50–75)	51 (50–75)	0	Murmur	17	20	7.3 (<3)	86.6 (75–90)	Expired
4	F	3.7 (75–90)	NA	2	NA	0	4	6.5 (25–50)	69.2 (>97)	Expired
5	M	3.09 (25–50)	50(25–50)	20	Myopia	44	100	23.7 (10–25)	135.7 (75–90)	Alive
6	F	2.9 (10–25)	49 (25–50)	3	Murmur	34	38	14.5 (50–75)	111 (>97)	Alive
7	M	3.31 (25–50)	53 (90–95)	0	Desaturation at birth	5	5	7.6 (25–50)	72.1 (95–97)	Alive
8	F	2.56 (3–5)	48 (25–50)	0	Prenatal US	0	0	2.7 (5–10)	48 (25–50)	Expired

NA, not available; US, ultrasonography.

in South Korea.

Materials and methods

Between 2004 and 2014, among the 180 patients who had been followed up for MFS during this period, eight patients were clinically diagnosed with infantile MFS at Seoul National University Hospital. Diagnosis of MFS was based on the revised Ghent criteria[4,7]. Systemic score is one of the diagnostic criteria and is calculated according to the most selective systemic features and the score greater than or equal to 7 points was considered a positive systemic score[4]. All available medical records were reviewed retrospectively, including gender, birth weight and height, age at diagnosis, follow-up duration, other systemic involvement, family history, echocardiographic findings, gene testing, operations, medications, and mortality. This study was approved by the Institutional Review Boards of Seoul National University Hospital (IRB number: H-1501-016-636), and informed consent was waived because of its retrospective nature.

Results

1. Demographic findings

Table 1 shows the demographic data of 8 patients (2 boys and 6 girls) with infantile MFS. Five patients had medical records reporting height at birth, and the median was 50.0 cm (range, 48–53 cm). Among these 5 patients, only one patient was taller than the 90th percentile of height at birth. Their ages at the time of diagnosis ranged from 0 to 20 months (median age, 2.5 months) and the median follow-up duration was 25.5 months (range, 0–94 months). The most common presenting symptom was a heart murmur, in three patients, and one patient was diagnosed *in utero*. At the time of this study, four of the 8 patients were taller than the 95th percentile of height.

Table 2. Revised Ghent nosology pattern in each of the patients with infantile Marfan syndrome

Case	Family history	Aorta ($z \geq 3$)	Ectopia lentis	*FBN1* gene mutation	Systemic score
1	Negative	35.4 mm (6.10)	NA	NA	6
2	Negative	NA	–	NA	NA
3	Negative	31.0 mm (7.57)	+	–	6
4	Negative	20.9 mm (5.02)	NA	+	3
5	Negative	32.4 mm (5.46)	+	+	13
6	Negative	25.1 mm (6.37)	+	+	6
7	Negative	16.5 mm (4.66)	–	+	2
8	Negative	13.8 mm (3.87)	NA	NA	4

NA, not available; *FBN1*, Fibrillin 1.

Three of the patients (cases 1, 2, and 4) were lost to follow-up at our hospital. By asking other hospital physicians and the statistical service of the Ministry of Government Administration and Home Affairs, we learned that two of these patients died during follow-up at other hospitals and one patient is still alive. Among the 5 patients who were followed up at our hospital, 3 patients are still alive, but the other 2 died during follow-up. One patient (case 3) died from heart failure despite several operations, including mitral valve replacement (MVR). This patient was referred to our hospital for myocarditis but she was diagnosed with decompensated heart failure due to mitral valve chordae rupture from MFS. The other patient (case 8) died from heart failure 3 days after birth despite intensive inotropic support. The median age of mortality was 12 months (range, 0–131 months).

All patients had no family history of MFS; however, MFS was suspected in the mother of one patient, though we did not perform genetic confirmation for this mother (Table 2). Among the eight patients, ophthalmic examination was performed on five, and three of these had lens subluxation. We performed a fibrillin 1 (*FBN1*) gene mutation test in 5 patients, and 4 of these were identified as having a *FBN1* gene mutation. There was only 1 patient whose systemic score of Ghent nosology was greater or

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Table 3. Cardiovascular complications and treatment of each of the patients with infantile Marfan syndrome

Case	MVP	MV annulus, mm (*z* score)	MR	TVP	TV annulus, mm (*z* score)	TR	Aortic annulus, mm (*z* score)	AR	CHF	Op.	Age at Op.	Medications at last follow-up
1	+	39.5 (4.10)	Severe	+	NA	Mild	24.2 (5.96)	Moderate	Present	1. MVR 2. Valve-sparing aortic root replacement 3. AVR	1.48 mo 2.5 yr 8 mo 3.8 yr 10 mo	SRN, CTP, DGX, CVD, FRS, WFR
2	+	NA	Severe	NA	NA	Moderate	NA	Mild	Present	-	-	ENL, DGX
3	+	30 (5.14)	Severe		NA	Moderate	NA	Trace	Present	1. MV repair, TV annuloplasty 2. MVR 3. Bilateral lensectomy 4. Lung volume reduction	1.3 mo 2.5 mo 3.8 mo 4.16 mo	DGX, FRS, SRN, LST, WFR, ENL
4	+	25.7 (3.76)	Severe	+	22.5 (1.81)	Moderate	13.6 (4.50)	None	Present	MVR	Less than 1 yr at other hospital	LST, FRS, SRN, PRN
5	+	37.4 (3.84)	Moderate	+	NA	Mild	19.9 (4.19)	Trace	Present	MVR	69 mo	WFR, ATN, LST
6	+	29.3 (4.42)	Moderate	+	NA	Mild	13.6 (4.13)	None	Present	MVR	9 mo	WFR, ATN, LST
7	+	14.8 (1.30)	Mild	+	12.8 (-0.22)	Moderate	9 (2.46)	Trace	None	-	-	ATN
8	+	13.9 (1.47)	Mild	+	17.3 (1.82)	Severe	8.7 (3.10)	Mild	Present	-	-	Inotropics

MV, mitral valve; MVP, mitral valve prolapse; MR, mitral regurgitation; TVP, tricuspid valve prolapse; TV, tricuspid valve; TR, tricuspid regurgitation; AR, aortic regurgitation; CHF, congestive heart failure; Op., operation; NA, not available; MVR, mitral valve replacement; AVR, aortic valve replacement; SRN, spironolactone; CTP, captopril; DGX, digoxin; CVD, carvedilol; FRS, furosemide; WFR, warfarin; ENL, enalapril; LST, losartan; PRN, propranolol; ATN, atenolol.

equal to 7 points. Dilatation of the aortic sinus diameter is defined as a *z* score greater than2[8]. One patient did not have echocardiographic records of aortic sinus diameter, and the *z* score of the other seven patients was greater than 2, with a median z value of 5.46 (range, 3.87–7.57).

2. Cardiovascular manifestations and treatment

All patients had mitral valve prolapse (MVP) and the z score of the mitral valve annulus in five of the seven patients who had accurate measurements of mitral valve annulus size was greater than 2 (Table 3). All patients had various degrees of mitral regurgitation (MR) at initial echocardiography. The MR was mild in 2 patients, moderate in 2 patients, and severe in 4 patients at the time of diagnosis.

Other than 1 patient who had no medical record of tricuspid valve findings from echocardiography, all of the patients had tricuspid valve prolapse. Only 3 patients had an echocardiographic record of the tricuspid valve annulus diameter and the *z* score was less than 2. All eight patients had various degrees of tricuspid regurgitation (TR). The TR was mild in 3 patients, moderate in 4 patients, and severe in 1 patient.

Six patients had medical records of aortic annulus diameter and all of them had an aortic annulus z score greater than 2. Six patients had aortic regurgitation (AR), and the AR was trivial in 3 patients, mild in 2 patients, and moderate in 1 patient. No patients had severe AR. There were seven patients with congestive heart failure before surgery or during follow-up.

Five patients underwent open-heart surgery, and MVR was performed in all cases at the median age of 28.5 months (range, 5–69 months). Among them, 2 patients needed multiple operations. One of these patients underwent MVR at a 4-year-old, a David operation at a 5.7-year-old, and aortic valve replacement at an 8.9-year-old. The other patient underwent mitral valve repair and tricuspid valve annuloplasty at the age of 3 months, and MVR at the age of 5 months. All patients except for the one who died at 3 days of age took multiple medications, including losartan and atenolol. The patients with congestive heart failure were also prescribed diuretics and digoxin.

Discussion

In our series of 8 cases of infantile MFS, most patients showed significant atrioventricular valve dysfunction and resulting congestive heart failure symptoms. Five patients required early MVR for heart failure symptoms. The prognosis of infantile MFS is very grave and half of infantile MFS patients showed mortality at the median age of 12 months in our series.

MFS is a systemic disorder of connective tissue. The prevalence of MFS has been estimated to be approximately 1–2 per 10,000 individuals without gender or ethnic differences; however, the true incidence is difficult to determine because the manifestations of the disease become more obvious with age[1,9,10].

A 5-year-old child who had congenital contractures, long extremities, and spider-like digits was first described by French pediatrician Antoine Marfan in 1896[11]. Later, involvements of the ocular and cardiovascular system were noted and the first diagnostic criteria for the disorder were established in 1988

(Berlin nosology)[12]. Currently, the diagnosis relies on features of the skeletal, ocular, cardiovascular, cutaneous, central nervous, and pulmonary systems in addition to family history and *FBN1* mutations[4,7].

Infantile or neonatal MFS is rarely diagnosed and is a type of MFS that is atypical and has a severe effect on the cardiovascular system[13]. In older or classic MFS, cardiovascular events leading to death are mostly aortic dissection or ruptures; however, deaths among neonatal MFS patients are associated with CHF due to MR or TR[14]. In addition, infantile MFS has higher mortality rate within the first year of life than classic MFS of which the mean age at death is 33.5 years of life[15,16]. It is considered to usually be caused by a new mutation, not because of a positive family history[15]. In our 8 patients, all patients had no definitive family history. One patient had suspected mother, but she had never been diagnosed with MFS.

Even though infantile MFS is rare and difficult to diagnose, there are clues as to whether a newborn has infantile MFS. If fetal ultrasound reveals cardiomegaly and marked valvular lesions, fetal echocardiography should be performed and cautiously examined for both, atrioventricular prolapse and aortic root dilatation[17]. In addition to the fetal echocardiography, length at birth can be a useful tool to evaluate infantile MFS. Erkula et al.[18] reported that the mean height at birth in MFS patients approached the 90th percentile of the general population in both males and females, suggesting that excessive growth in MFS patients begins prenatally. However, among the 5 patients for whom we found height at birth data in our series, only 1 patient showed greater than 90 percentile of height. Congenital emphysema is also common in neonatal MFS and the syndrome can be suspected when a neonate presents pulmonary emphysema with typical manifestations[5,19,20]. A characteristic phenotype of affected infants includes an aged face, arachnodactyly, dolichocephaly, high-arched palate, micrognathia, joint hyperflexibility, joint

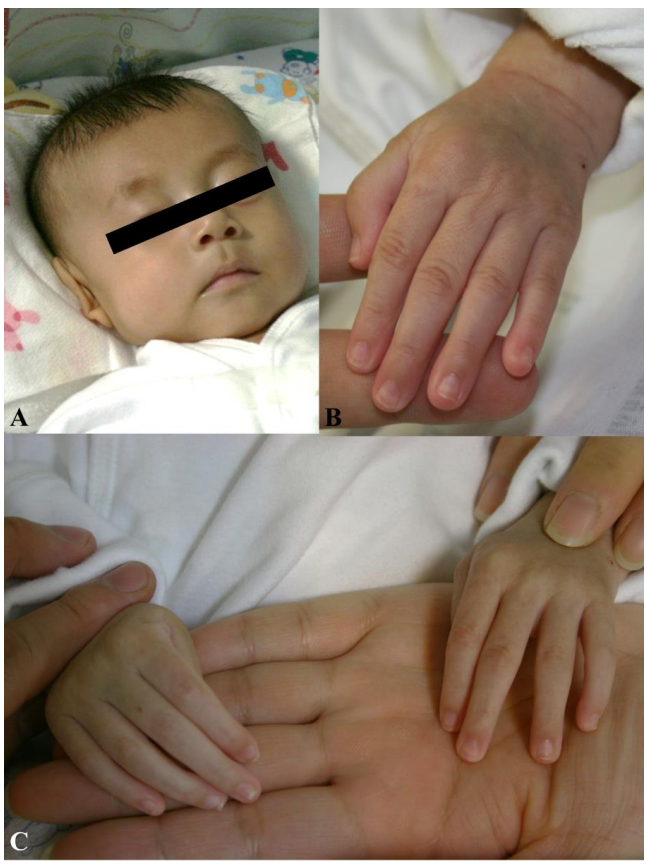

Fig. 1. Case 3. (A) Dolichocephaly. (B, C) Arachnodactyly of the hands at 5 months of age.

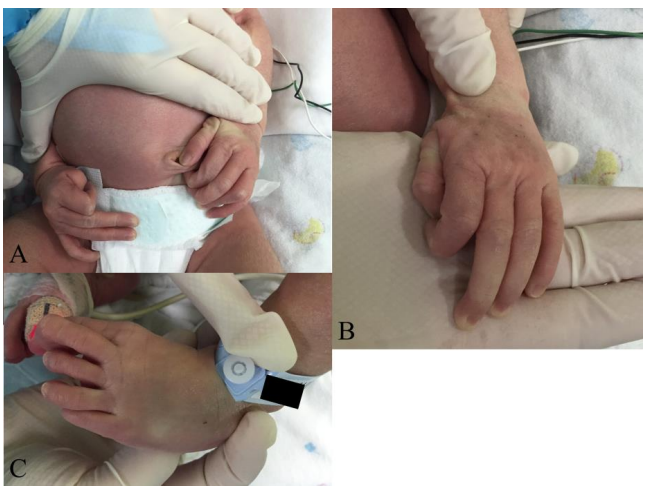

Fig. 2. Case 7. (A) Loose skin and arachnodactyly. (B, C) Arachnodactyly of the hand and foot at 14 days of age.

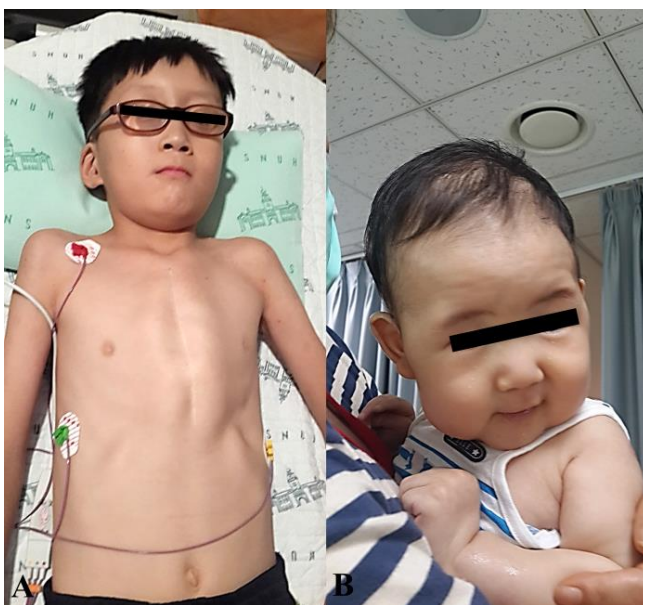

Fig. 3. Aged face. (A) Case 5 at 130 months old and (B) case 7 at age 5 months of age.

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contractures, pes planus, and chest deformity, as seen in our patients[3] (Figs. 1-3).

The prognosis of infantile MFS diagnosed during the first year of life is known to be poor. The life span of infantile MFS patients is expected to be less than 2 years because of the severity of the cardiovascular problems[15]. The majority of these patients require both medical and surgical management, and the available medical and surgical strategies for patients with MFS are directed towards prevention of cardiovascular complications[21]. Beta blocking agents are currently recommended for early use by MFS patients[22]. In pediatric MFS patients, beta blockers are known to delay cardiac interventions. However, in infant MFS patients, the benefits of using beta blocker are not known[3,23,24]. Infants with MFS who have atrioventricular valve insufficiencies usually require digoxin and/or diuretics to prevent congestive heart failure; this was similar to the requirement in our patients. In spite of using multiple medications, valve surgery is generally necessary because moderate or severe MR associated with left ventricular volume overload provokes congestive heart failure and may lead to sudden cardiac death[22]. Both mitral valve repair and/or replacement can be an option for surgical treatment; however, the outcome data on valve surgery are limited in patients with infantile MFS. Furthermore, there is a high probability of mortality and morbidity including complete heart block, thrombosis, and stroke after valve surgery[25-27]. In our study, three patients died despite MVR.

Because of potential new therapies and proper explanation to the parents, it is increasingly important to recognize infantile MFS prenatally in addition to shortly after birth in order to perform diagnostic work-up and initiate appropriate management in a timely fashion[28].

In conclusion, because the prognosis of infantile MFS is very grave, early detection and a timely cautious treatment is essential to prevent further morbidity and mortality.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Judge DP, Dietz HC. Marfan's syndrome. Lancet 2005;366:1965-76.
2. Dietz HC, Cutting GR, Pyeritz RE, Maslen CL, Sakai LY, Corson GM, et al. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. Nature 1991;352:337-9.
3. Morse RP, Rockenmacher S, Pyeritz RE, Sanders SP, Bieber FR, Lin A, et al. Diagnosis and management of infantile marfan syndrome. Pediatrics 1990;86:888-95.
4. Loeys BL, Dietz HC, Braverman AC, Callewaert BL, De Backer J, Devereux RB, et al. The revised Ghent nosology for the Marfan syndrome. J Med Genet 2010;47:476-85.
5. Hennekam RC. Severe infantile Marfan syndrome versus neonatal Marfan syndrome. Am J Med Genet A 2005;139:1.
6. Geva T, Sanders SP, Diogenes MS, Rockenmacher S, Van Praagh R. Two-dimensional and Doppler echocardiographic and pathologic characteristics of the infantile Marfan syndrome. Am J Cardiol 1990;65:1230-7.
7. 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.
8. van Kimmenade RR, Kempers M, de Boer MJ, Loeys BL, Timmermans J. A clinical appraisal of different Z-score equations for aortic root assessment in the diagnostic evaluation of Marfan syndrome. Genet Med 2013;15:528-32.
9. Cañadas V, Vilacosta I, Bruna I, Fuster V. Marfan syndrome. Part 1: pathophysiology and diagnosis. Nat Rev Cardiol 2010;7:256-65.
10. Pearson GD, Devereux R, Loeys B, Maslen C, Milewicz D, Pyeritz R, et al. Report of the National Heart, Lung, and Blood Institute and National Marfan Foundation Working Group on research in Marfan syndrome and related disorders. Circulation 2008;118:785-91.
11. Marfan AB. Uncas de déformationcongénitale des quatremembres, plus prononcée aux extrémités, caractériséeparl'allongement des os avec un certaindegréd'amincissement. Bull Mem Soc Med Hop (Paris) 1896;13:220-6.
12. Beighton P, de Paepe A, Danks D, Finidori G, Gedde-Dahl T, Goodman R, et al. International Nosology of Heritable Disorders of Connective Tissue, Berlin, 1986. Am J Med Genet 1988;29:581-94.
13. Das R, Majumder B, Bera D, Chakraborty S. Neonatal Marfan syndrome: a rare presentation. Niger J Cardiol 2015;12:57-9.
14. Pyeritz RE, Wappel MA. Mitral valve dysfunction in the Marfan syndrome. Clinical and echocardiographic study of prevalence and natural history. Am J Med 1983;74:797-807.
15. Shih HY, Liu WS, Chen TJ. Neonatal Marfan syndrome: a case report. Acte Cardiol Sin 2004;20:171-5.
16. Phornphutkul C, Rosenthal A, Nadas AS. Cardiac manifestations of Marfan syndrome in infancy and childhood. Circulation 1973;47:587-96.
17. Ramaswamy P, Lytrivi ID, Nguyen K, Gelb BD. Neonatal Marfan syndrome : in utero presentation with aortic and pulmonary artery dilatation and successful repair of an acute flail mitral valve leaflet in infancy. Pediatr Cardiol 2006;27:763-5.
18. Erkula G, Jones KB, Sponseller PD, Dietz HC, Pyeritz RE. Growth and maturation in Marfan syndrome. Am J Med Genet 2002;109:100-15.
19. Day DL, Burke BA. Pulmonary emphysema in a neonate with Marfan syndrome. Pediatr Radiol 1986;16:518-21.
20. Shinawi M, Boileau C, Brik R, Mandel H, Bentur L. Splicing mutation in the fibrillin-1 gene associated with neonatal Marfan syndrome and severe pulmonary emphysema with tracheobronchomalacia. Pediatr Pulmonol 2005;39:374-8.
21. Canadas V, Vilacosta I, Bruna I, Fuster V. Marfan syndrome. Part 2: treatment and management of patients. Nat Rev Cardiol 2010;7:266-76.
22. Keane MG, Pyeritz RE. Medical management of Marfan syndrome. Circulation 2008;117:2802-13.
23. Buchhorn R, Kertess-Szlaninka T, Dippacher S, Hulpke-Wette M. Neonatal Marfan syndrome: improving the bad prognosis with a strict conservative treatment with carvedilol? Open J Thorac Surg

2014;4:44-7.
24. Lacro RV, Dietz HC, Sleeper LA, Yetman AT, Bradley TJ, Colan SD, et al. Atenolol versus losartan in children and young adults with Marfan's syndrome. N Engl J Med 2014;371:2061-71.
25. Kim ER, Kim WH, Choi ES, Cho S, Jang WS, Kim YJ. Surgical management of mitral regurgitation in patients with Marfan syndrome during infancy and early childhood. Korean J Thorac Cardiovasc Surg 2015;48:7-12.
26. Miyahara Y, Kasahara S, Takagaki M, Sano S. Successful aortic reimplantation in a three-year-old child with Marfan syndrome. Interact Cardiovasc Thorac Surg 2010;11:218-20.
27. Strigl S, Quagebeur JM, Gersony WM. Quadrivalvar replacement in infantile Marfan syndrome. Pediatr Cardiol 2007;28:403-5.
28. Sutherell J, Zarate Y, Tinkle BT, Markham LW, Cripe LH, Hyland JC, et al. Novel fibrillin 1 mutation in a case of neonatal Marfan syndrome: the increasing importance of early recognition. Congenit Heart Dis 2007;2:342-6.

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