Case Report
Volume 13:1, 2025

Journal of Cardiovascular Diseases & Diagnosis

ISSN: 2329-9517 Open Access

Neonatal Marfan Syndrome: A Case Report of Unusual Findings

Soodeh Hooshmandi*, Sina Habibzadeh, Hamed Abbasizadehghoroghchi and Majid Sadeghi

Department of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Neonatal Marfan Syndrome (nMFS) is an autosomal dominant fibrous connective tissue disorder caused by a mutation in the Fibrillin-1 gene (*FBN1*). This condition mostly affects the cardiovascular, ophthalmic, and skeletal systems. The most specific symptom of nMFS is a rapidly progressive cardiovascular disease that, the majority cases of which lead to mortality in the first years of life.

Case report: We present a new case of nMFS that led to the death of the patient within the first months of her life. A post-study was conducted based on the suspicion of nMFS after the patient's death. Genetic studies revealed mutations in *FBN1* Exon 26, *FLVCR*1 Exon 4, *ARSB* Exon 1, *LARS1* Exon 32, and *SCO2* Exon 2. Mutation in *FBN1* leads to nMFS, which explained the symptoms of the patient. Severe cardiorespiratory distress was the reason for the patient's death.

Discussion: Based on the study findings, it can be stated that examining other gene mutations in nMFS will be necessary in case of unusual findings that do not match nMFS.

Keywords: Neonatal Marfan syndrome • *FBN1* • ASD • Severe cardiorespiratory distress • Patient

Introduction

Marfan syndrome (OMIM #154700) is an autosomal dominant condition affecting connective tissues in numerous organs such as the cardiovascular, skeletal, pulmonary, and ocular systems. The fundamental pathogenic cause of this condition is the fibrillin-1 malfunction, which is an extracellular matrix protein composed of connective tissue micro fibrils [1]. The cardiovascular, ocular, and skeletal systems are the most impacted by this illness, with the cardinal manifestations being:

- Aortic aneurysm with dissection,
- Ectopic lentils, and
- Long-bone overgrowth.

This syndrome is known for its diverse manifestations, the severity of clinical symptoms, age of onset, and targeted organs. No cardiac symptoms may be more pronounced than cardiac symptoms in some cases. Infantile pulmonary emphysema is also more common in nMFS, whereas aortic and aortic root pathology is more common in classical Marfan syndrome [2,3]. An international expert group has developed a revised Ghent nosology that highlights cardiovascular signs and specifies aortic root aneurysm and ectopic lentils as the key clinical criteria [4]. nMFS can manifest in the prenatal period and is distinguished at birth by some additional characteristics not shared by the classic form. Flexion contractures, typical facial dysmorphology (crumpled ears, loose superfluous skin, and a characteristic "senile" facial expression), pulmonary emphysema, and serious cardiovascular illness are among such characteristics [5]. According to the revised Ghent nosology, the studied patient received a score of 6, but a high suspicious genetic test was performed and validated the diagnosis. When compared to classical and incomplete MFS, nMFS is an uncommon syndrome with the most severe phenotype and the worst prognosis; its prevalence is far lower than that estimated for MFS, *i.e.* 1/5,000 to 1/10,000. Exons 24–32 of FBN1 frequently segregate in patients with nMFS, making this area of FBN1 a key locus for nMFS [6]. nMFS can be caused by mutations outside of this region, but this has only been described three times, based on the literature: Twice in exon 4 and once in exon 21 [7,8]. Exons 25-26

***Address for Correspondence:** Soodeh Hooshmandi, Department of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran, Tel: 9228595842; E-mail: S.hooshmandi12@gmail.com*

Received: 05 August, 2023, Manuscript No. JCDD-23-109405; **Editor assigned:** 08 August, 2023, PreQC No. JCDD-23-109405 (PQ); **Reviewed:** 23 August, 2023, QC No. JCDD-23-109405; **Revised:** 22 January, 2025, Manuscript No. JCDD-23-109405 (R); **Published:** 29 January, 2025, DOI: 10.37421/2329-9517.2025.13.636

mutations are overrepresented and are linked to decreased survival in children diagnosed with *FBN1* mutations before the age of one year [7]. Functional pulmonary atresia is an uncommon sign of nMFS that has been documented only once [9]. Other atypical findings in nMFS include ASD and PDA, which are more common in Loeys-Dietz syndrome [10]. Our studies revealed three more cases of ASD in nMFS [5,11]. This paper reported the early diagnosis and therapy of a child with nMFS who was suffering from severe mitral and tricuspid valve insufficiency, aortic root dilatation, and PPHN. The patient was admitted to Amir Hospital after echocardiography revealed aortic root dilatation at a gestational age of 18 weeks. Aortic root dilatation was confirmed by additional testing (6.5 mm). In addition to aortic root dilatation, arachnodactyly was discovered by a 25 weeks ultrasound. The patient showed dysmorphic facial features at birth, indicating nMFS. When she aged 4 months, echocardiography indicated cardiomegaly, mitral and tricuspid valve regurgitation, type-2 ASD, and ascending aorta dilatation of approximately 11 mm. The detection of a pathogenic mutation in the *FBN1* gene using direct sequencing of exon 25 aids in the diagnosis field [12]. A mutation in exon 26 of the c.3143T>C gene confirmed the diagnosis. Because the mutation was not found in her parents, the child was one of the 25% of sporadic cases of MFS. This clinical appearance lends credence to the assumption that spontaneous instances are more seriously impacted than family cases [6]. The studied patient died as a result of cardiorespiratory discomfort. It can be concluded that this brief review study will be useful for clinical diagnosis and patient management in order to minimize future issues such as refractory heart failure in such patients.

Case Presentation

We report a 7-month-old girl who died of cardiorespiratory distress due to nMFS. The mother and father of this patient were a 23-year-old housewife and a 28-year-old carpenter. The parents were relatives (they were cousins) and reported no familial history of heredity disorders. They were living in Semnan, Iran. The pregnancy was affected by no specific disease, such as thyroid disease, hypertension, diabetes, and infections, drugs, or exposure to toxins. Aortic root dilatation found on ultrasonography at a gestational age of 18 weeks led to an antenatal referral to Amir Hospital's pediatric department. At the gestational age of 18 weeks, echocardiography indicated aortic root dilatation of 6.5 mm (Figure 1).

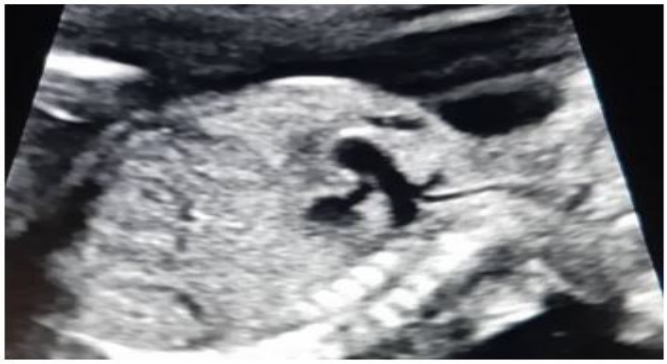

Figure 1. 18-week echocardiogram showed aortic root dilation=6.5 mm.

The same diameter of dilation was detected in echocardiography in the 19th week. The 25-week ultrasound revealed arachnodactyly of both fingers and toes, as well as aortic dilatation. The patient was born full-term through vaginal delivery without any complications. She weighed 2.9 kg at birth. Post-birth physical examinations revealed severe hypotonic, dysmorphic facial features, craniosynostosis, flexion contracture of the wrist and hip joints, and arachnodactyly (Figure 2).

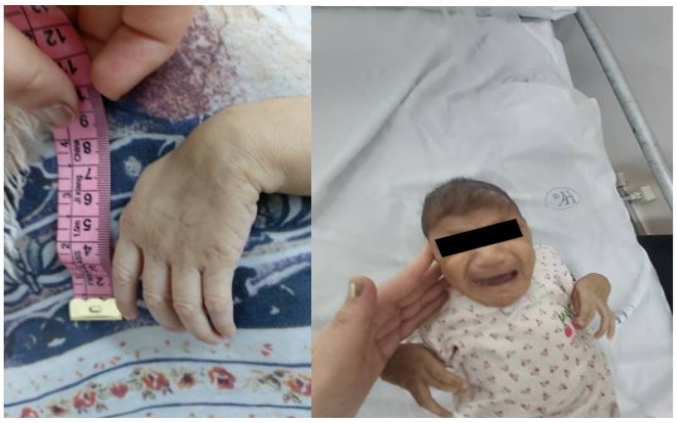

Figure 2. Dysmorphic facial features and wrist flexion contracture.

The patient was taken to the hospital due to acute hypotonic. A systolic murmur was discovered on physical examination, and echocardiography revealed moderate LAE, LVE, mild to moderate RAE, mild RVE, and LVEF=55 mm, ASD2 with redundant IAS, minor apical. mus. VSD, and mitral and tricuspid valve regurgitation (Figure 3).

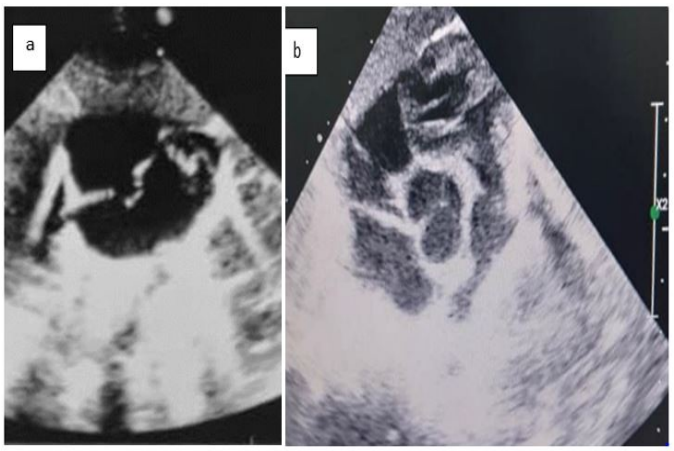

Figure 3. 20-Days echocardiogram is showing: a) ASD2 b) moderate to severe MR, MVP, and PPG=45 mmHg.

The patient was readmitted to the hospital due to respiratory distress and failure to thrive when she aged four months. Physical examinations revealed hypotonic, crackles in both lungs, and the same findings as at birth. CXR also showed cardiomegaly (Figure 4).

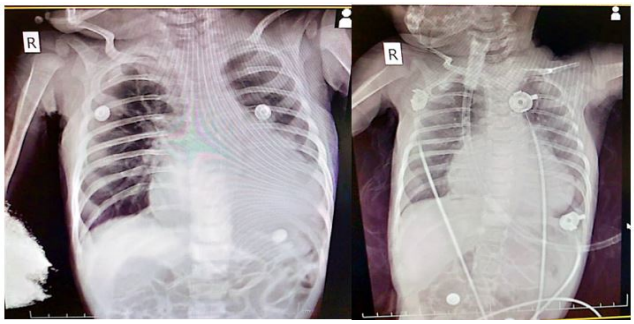

Figure 4. CXR showed massive cardiomegaly.

In addition, echocardiography revealed moderate to severe RAE, MVP, tricuspid valve prolapses, ASD type 2, and moderate mitral regurgitation. The patient was readmitted three months later due to increased respiratory discomfort and cough. Physical examinations revealed that the patient was severely suffering from distress, pulmonary hypertension, pulmonary artery dilatation, and cardiomegaly. She was clinically diagnosed with congestive heart failure, which was treated with furosemide, captopril, and fluid restriction. We had no choice but to intubate the patient on the second day due to deteriorating heart failure and respiratory discomfort caused by severe hypotonic. On the fifth day, the patient collapsed and CPR was performed. Despite receiving a large dose of intravenous inotropic (dobutamine) medication, the patient died on the sixth day of admission due to severe cardiorespiratory discomfort. The patient had a de novo mutation of *FBN1* Exon 26, c.3143T>C, *FLVCR1* Exon 4, *ARSB* Exon 1, *LARS1* Exon 32, and *SCO2* Exon 2, which causes ataxia, mucopolysaccharidosis type VI, infantile liver failure syndrome, and mitochondrial complex IV. To the best of our knowledge, this is an unprecedented association of gene mutations.

Discussion

The case presented highlights the severity of neonatal Marfan Syndrome (nMFS) and the challenges in managing this condition. nMFS is a rare and severe form of Marfan syndrome, with a prevalence estimated to be much lower than that of classical Marfan syndrome. The diagnosis of nMFS can be challenging due to the diverse manifestations and severity of clinical symptoms, as well as the age of onset and targeted organs.

Early diagnosis and appropriate management are crucial in minimizing the complications associated with nMFS. In this case, the patient was diagnosed early in life, and appropriate therapy was initiated. However, despite the therapy, the patient died due to cardiorespiratory discomfort, highlighting the challenges in managing this condition.

The management of nMFS involves a multidisciplinary approach, including medical, surgical, and genetic interventions. Medical management includes the use of medications such as beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers to control blood pressure and prevent aortic dissection. Surgical interventions, such as aortic root replacement, may be required in severe cases. Genetic counselling and testing are also essential in the management of nMFS, as it can help identify the specific mutations responsible for the condition and guide family planning.

The pathogenesis of nMFS is not fully understood, and further research is needed to identify the underlying mechanisms and develop targeted therapies. Advances in genetic testing and gene therapy may provide new treatment options for this rare and severe condition.

Conclusion

In conclusion, nMFS is a rare and severe form of Marfan syndrome, and early diagnosis and appropriate management are crucial in minimizing complications. A multidisciplinary approach involving medical, surgical, and genetic interventions is essential for the management of nMFS. Further research is needed to improve our understanding of the pathogenesis and develop targeted therapies for this challenging condition.

Patient Consent

The patient's parents completed an informed consent form before her data was published.

Informed Consent

All participants in the study expressed their informed consent.

Conflict of Interest

The authors have no conflict of interest to disclose.

Funding Declaration

No funding was secured for this study.

Contributorship Statement

Soode Hoshmandi and Sina Habibzadeh and Hamed Abbasizadehghoroghchi conceptualized and designed the study, drafted the initial manuscript, participated in the case management, collected data, reviewed the research literature, performed histopathological studies and genetic analysis, and critically reviewed and revised the manuscript.

Majid Sadeghi performed imaging (echocardiography, prenatal ultrasound, and patient pictures, respectively) and revised the manuscript.

All authors agreed to be held accountable for all parts of the work and approved the final manuscript as submitted.

References

1. Maeda, Jun, Kenjiro Kosaki, Junko Shiono, and Kazuki Kouno, et al. "Variable severity of cardiovascular phenotypes in patients with an early-onset form of Marfan syndrome harboring FBN1 mutations in exons 24–32." *Heart Vessels* 31 (2016): 1717-1723.
2. Morse, Richard P, Sol Rockenmacher, Reed E Pyeritz, and Stephen P Sanders, et al. "Diagnosis and management of infantile Marfan syndrome." *Pediatrics* 86 (1990): 888-895.
3. Revencu, Nicole, Genevieve Quenum, Thierry Detaille, and Gaston Verellen, et al. "Congenital diaphragmatic eventration and bilateral uretero-hydronephrosis in a patient with neonatal Marfan syndrome caused by a mutation in exon 25 of the FBN1 gene and review of the literature." *Eur J Pediatr* 163 (2004): 33-37.
4. Loeys, Bart L, Harry C Dietz, Alan C Braverman, and Bert L Callewaert, et al. "The revised Ghent nosology for the Marfan syndrome." *J Med Genet* 47 (2010): 476-485.
5. Carande, Elliott J, Samuel J Bilton, and Satish Adwani. "A case of neonatal Marfan syndrome: a management conundrum and the role of a multidisciplinary team." *Case Rep Pediatr* 2017 (2017): 8952428.
6. Putnam, Elizabeth A, Mimi Cho, Arthur B Zinn, and Jeffrey A Towbin, et al. "Delineation of the Marfan phenotype associated with mutations in exons 23–32 of the FBN1 gene." *Am J Med Genet* 62 (1996): 233-242.
7. Stheneur, Chantal, Laurence Faivre, Gwenaelle Collod-Beroud, and Elodie Gautier, et al. "Prognosis factors in probands with an FBN1 mutation diagnosed before the age of 1 year." *Pediatr Res* 69 (2011): 265-270.
8. Tiecke, Frank, Stefanie Katzke, Patrick Booms, and Peter N Robinson, et al. "Classic, atypically severe and neonatal Marfan syndrome: twelve mutations and genotype–phenotype correlations in FBN1 exons 24–40." *Eur J Hum Genet* 9 (2001): 13-21.
9. Andelfinger, G, Girish S Shirali, RA Raunikar, and AM Atz, et al. "Functional pulmonary atresia in neonatal Marfan's syndrome: successful treatment with inhaled nitric oxide." *Pediatr Cardiol* 22 (2001): 525-526.
10. Loeys, Bart L, Ulrike Schwarze, Tammy Holm, and Bert L Callewaert, et al. "Aneurysm syndromes caused by mutations in the TGF-β receptor." *N Engl J Med* 355 (2006): 788-798.
11. Geva, Tal, Stephen P Sanders, Maria S Diogenes, and Sol Rockenmacher, et al. "Two-dimensional and Doppler echocardiographic and pathologic characteristics of the infantile Marfan syndrome." *Am J Cardiol* 65 (1990): 1230-1237.
12. Ng, DK, KW Chau, C Black, and TMM Thomas, et al. "Neonatal Marfan syndrome: a case report." *J Paediatr Child Health* 35 (1999): 321-323.

How to cite this article: Hooshmandi, Soodeh, Sina Habibzadeh, Hamed Abbasizadehghoroghchi and Majid Sadeghi. "Neonatal Marfan Syndrome: A Case Report of Unusual Findings." *J Cardiovasc Dis Diagn* 13 (2025): 636.